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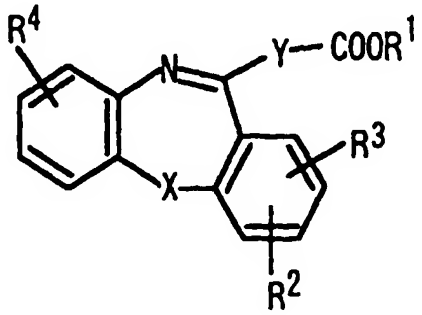
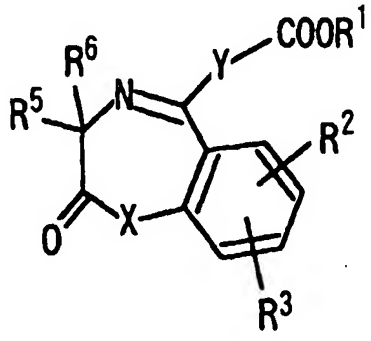
(54) COMPOUNDS POTENTIATING RETINOID

(57) A compound represented by the general formula (I) or (II) wherein R^1 represents hydrogen atom or a C_{1-6} alkyl group; R^2 and R^3 represent hydrogen atom or a C_{1-6} alkyl group, or R^2 and R^3 together represent a 5- or 6-membered cycloalkyl group; R^4 represents hydrogen atom, a C_{1-6} alkyl group or the like; R^5 represents hydrogen atom, a C_{1-6} alkyl group or the like; R^6 represents hydrogen atom or a C_{1-6} alkyl group; X represents $-NR^7-$, -O-, $-CHR^7-$ or -S- where R^7 represents hydrogen atom, a C_{1-6} alkyl group or the like; and Y represents a phenylene group or a pyridinediyl group, or a salt thereof. The compound of the present invention is useful as an agent for enhancing the activity of a retinoid compound.





EP 0 906 907 A1

Description

Technical Field

[0001] The present invention relates to novel compounds, and it relates to novel compounds which enhance the physiological activity of the ligands to intranuclear receptors whose typical examples include retinoic acid and compounds having retinoic acid-like physiological actions (retinoids).

Background Art

[0002] Retinoic acid (vitamin A acid), an active metabolite of vitamin A, has extremely important physiological functions, e.g., inducing differentiation of immature cells under development processes toward mature cells having specific functions, enhancement of cell proliferation, and life support action. It has been revealed that various vitamin A derivatives synthesized so far also have similar physiological functions, for example, the benzoic acid derivatives disclosed in Japanese Patent Unexamined Publication (KOKAI) Nos. (Sho)61-22047/1986 and (Sho)61-76440/1986, and the compounds described in Journal of Medicinal Chemistry, 1988, Vol. 31, No. 11, p.2182. "Retinoids" is a general term for retinoic acid and the aforementioned compounds having retinoic acid-like biological activities.

[0003] For example, it was proved that all-trans retinoic acid binds as a ligand to the retinoic acid receptor (RAR) present in cell nuclei, which belongs to the intranuclear receptor super family (Evans, R.M., Science, 240, p.889, 1988), and regulates proliferation and differentiation of animal cells or cellular mortalities (Petkovich, M., et al., Nature, 330, pp.444-450, 1987). It has also been suggested that the aforementioned compounds having the retinoic acid-like biological activities, e.g., 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid: Am80, also bind to RAR in similar manners to retinoic acid to exhibit their physiological actions (see, Hashimoto, Y., Cell Struct. Funct., 16, pp.113-123, 1991; Hashimoto, Y., et al., Biochem. Biophys. Res. Commun., 166, pp.1300-1307, 1990). Clinically, these compounds were found as useful for the therapeutic and preventive treatment of vitamin A deficiency disease, hyperkeratosis of epithelial tissue, rheumatism, delayed allergy, bone disease, leukemia and certain types of cancer.

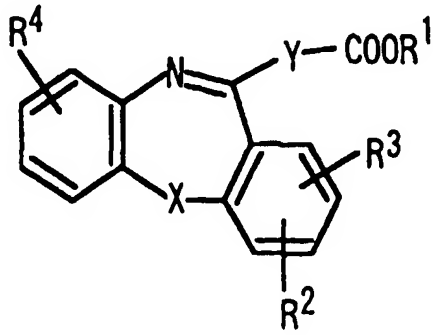
[0004] Compounds which antagonize against these retinoids and reduce the primary actions of the retinoid are known (Eyrolles, L., et al., Journal of Medicinal Chemistry, 37(10), pp.1508-1517, 1994). However, any compound has not been known, other than those disclosed in EP 694,301 A1, which enhances the actions of the retinoids such as retinoic acid, while the compound, per se, has no retinoid action or its retinoid actions are negligible. In this publication, it is suggested that a ligand compound specific to RXR receptor has an enhancing activity on Am80, i.e., a ligand compound specific to RAR-α-receptor.

Disclosure of the Invention

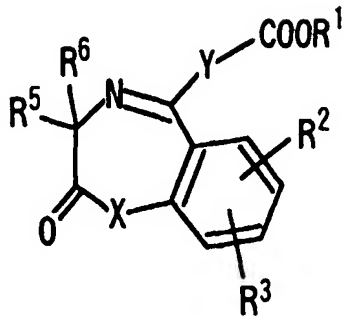
[0005] An object of the present invention is to provide compounds having enhancing activities on the actions of the retinoids such as retinoic acid. More specifically, the object of the present invention is to provide compounds which can markedly enhance the action of retinoids such as retinoic acid, while the compounds, per se, have no retinoid action or their retinoid actions are very weak.

[0006] The inventor of the present invention conducted various studies to achieve the foregoing object, and as a result, found that the compounds represented by the general formulas set out below enhance the action of retinoids such as retinoic acid. The present invention was achieved on the basis of the findings.

[0007] The present invention thus provides compounds represented by the following general formula (I):



or the following general formula (II) or salts thereof:



wherein, R^1 represents hydrogen atom or a C_{1-6} alkyl group; R^2 and R^3 independently represent hydrogen atom or a C_{1-6} alkyl group, or R^2 and R^3 may combine together with the carbon atoms of the phenyl ring to which R^2 and R^3 bind to represent a 5- or 6-membered cycloalkyl group which may optionally be substituted with one or more C_{1-4} alkyl groups; R^4 represents hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, hydroxyl group, nitro group, or a halogen atom; R^5 represents hydrogen atom, a C_{1-6} alkyl group, or an aryl-substituted C_{1-6} alkyl group; R^6 represents hydrogen atom or a C_{1-6} alkyl group; X represents $-NR^7-$, -O-, $-CHR^7-$ or -S- in which R^7 represents hydrogen atom, a C_{1-6} alkyl group, or an aryl-substituted C_{1-6} alkyl group; and Y represents a phenylene group or a pyridinediyl group.

[0008] In addition, according to further embodiments of the present invention, there are provided a medicament comprising the aforementioned compounds; and an agent enhancing the actions of the retinoid and an agent enhancing the actions of the ligands to the intranuclear receptors, said agents comprise the aforementioned compounds.

The Most Preferred Embodiments to Carry Out the Invention

[0009] In the above general formula (I), R^1 represents hydrogen atom or a linear or branched C_{1-6} (i.e., having 1 to 6 carbon atoms) alkyl group. Examples of the alkyl group include, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group, and tert-butyl group, and methyl group is preferably used.

[0010] R^2 and R^3 independently represents hydrogen atom or a linear or branched C_{1-6} alkyl group. As for the alkyl group, those mentioned above may be used, and ethyl group, isopropyl group, tert-butyl group or the like may preferably be used. The substituting positions of R^2 and R^3 are not particularly limited, and each of them may independently substitute at any position. However, it is preferred that R^2 and R^3 are at para-position and meta-position with reference to X, respectively, or R^2 and R^3 are at meta-position and ortho-position with reference to X. It is particularly preferred that R^2 and R^3 are at para-position and meta-position with reference to X, respectively.

[0011] R^2 and R^3 may combine to form a 5- or 6-membered cycloalkyl ring together with two carbon atoms on the phenyl ring to which R^2 and R^3 respectively bind. The cycloalkyl ring may have one or more C_{1-4} alkyl groups. For example, the ring may have from two to four methyl groups, preferably four methyl groups. It is preferred that, for example, R^2 and R^3 together with the phenyl ring substituted with R^2 and R^3 form 5,6,7,8-tetrahydronaphthalene ring or 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene ring.

[0012] R^4 represents hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, hydroxyl group, nitro group, or a halogen atom. As the C_{1-6} alkyl group, these exemplified above may be used. As the C_{1-6} alkoxy group, for example, methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, sec-butoxy group, or tert-butoxy group, preferably methoxy group, may be used. As the halogen atom, any of fluorine atom, chlorine atom, bromine atom, or iodine atom may be used. The position of R^4 is not particularly limited, and it may substitute at any position on the phenyl ring.

[0013] R^5 represents hydrogen atom, a C_{1-6} alkyl group, or an aryl-substituted C_{1-6} alkyl group. The C_{1-6} alkyl group may be either linear or branched, and those mentioned above may preferably be used. Examples of the aryl moiety of the aryl-substituted C_{1-6} alkyl group include, for example, phenyl, naphthyl, or pyridyl group, and the C_{1-6} alkyl moiety may be either linear or branched. For example, a phenyl-substituted C_{1-6} alkyl group such as benzyl group or phenethyl group, a naphthyl-substituted C_{1-6} alkyl group such as naphthylmethyl group, a pyridyl-substituted C_{1-6} alkyl group such as pyridylmethyl group and the like can be used.

[0014] The aryl group constituting these aryl-substituted C_{1-6} alkyl groups may have one or more substituents. For example, a halogen atom such as fluorine atom or chlorine atom; a C_{1-6} alkyl group such as methyl group or ethyl group; a linear or branched C_{1-6} alkoxy group such as methoxy group or ethoxy group; nitro group; a linear or branched halogenated C_{1-6} alkyl group such as trifluoromethyl group; hydroxyl group; carboxyl group; a C_{1-6} alkoxycarbonyl

group such as methoxycarbonyl group or ethoxycarbonyl group or the like may be used as the substituent. R^6 represents hydrogen atom or a C_{1-6} alkyl group. The C_{1-6} alkyl group may be either linear or branched, and those explained above may preferably be used. The compounds wherein both of R^5 and R^6 are hydrogen atoms, and the compounds wherein R^5 is a C_{1-6} alkyl group or an aryl-substituted C_{1-6} alkyl group and R^6 is hydrogen atom are particularly preferred compounds.

[0015] X represents a nitrogen atom substituted with R^7 (-NR^7-), an oxygen atom (-O-), a methylene group substituted with R^7 (-CHR^7-), or a sulfur atom (-S-). R^7 represents hydrogen atom, a C_{1-6} alkyl group, or an aryl-substituted C_{1-6} alkyl group. The C_{1-6} alkyl group may be either linear or branched, and those exemplified above, e.g., methyl group, may be used. As the aryl-substituted C_{1-6} alkyl group, those exemplified above, preferably benzyl group, may be used. The nitrogen atom and the sulfur atom may be in the form of N-oxide and sulfoxide, respectively. Among them, X is preferably a nitrogen atom substituted with R^7 (NR^7), and X most preferably represents a nitrogen atom substituted with methyl group, ethyl group, n-propyl group, isopropyl group, or benzyl group.

[0016] Y represents a phenylene group or a pyridinediyl group. For example, any one of phenylene groups or pyridinediyl groups such as p-phenylene group, m-phenylene group, o-phenylene group, pyridine-2,4-diyl group, pyridine-2,5-diyl group, or pyridine-3,5-diyl group may be used. Preferably, p-phenylene group, m-phenylene group, or pyridine-2,5-diyl group may be used. Where pyridine-2,5-diyl group is used, the group represented by -$COOR^1$ may substitute either at 2-position or 5-position of the pyridine ring.

[0017] Acid addition salts and base addition salts fall within the scope of the compounds of the present invention. Examples of the acid addition salts include mineral acid salts such as hydrochloride or hydrobromide, and organic acid salts such as p-toluenesulfonate, methanesulfonate, oxalate, or tartrate. The base addition salts may be formed when R^1 represents hydrogen atom. Metal salts such as, for example, sodium salt, potassium salt, magnesium salt, or calcium salt, ammonium salts, or organic amine salts such as, for example, triethylamine salt or ethanolamine salt, for example, may be used.

[0018] As for the compounds of the present invention represented by the formula (II), where R^5 and R^6 are different substituents to each other, the carbon atom substituted thereby is recognized as an asymmetric carbon atom. On the assumption that, in the formula (II), the 7-membered ring containing X forms a plane, either R^5 or R^6 may be above the plane. In addition, the compounds of the formula (I) and the formula (II) of the present invention may have one or more additional asymmetric carbon atoms depending on types of X and other substituents. Any optical isomers based on the asymmetric carbon atom(s), any mixture of optical isomers, racemates, any diastereomers based on two or more asymmetric carbons, any mixtures of the diastereomers and the like fall within the scope of the present invention. It should also be understood that any hydrates or solvates of the compounds in the free forms or those of the compounds in the forms of salts also fall within the scope of the present invention.

[0019] Among the compounds of the present invention represented by the above formula (I), preferred examples include:

4-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl]benzoic acid (HX600);
4-[5H-2,3-diisopropyl-5-methyldibenzo[b,e][1,4]diazepin-11-yl]benzoic acid (HX610);
4-[5H-2-tert-butyl-5-methyldibenzo[b,e][1,4]diazepin-11-yl]benzoic acid (HX511);
4-[5H-3,4-(1,4-butano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl]benzoic acid (HX545);
4-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyl-8-nitrodibenzo[b,e][1,4]-diazepin-11-yl]benzoic acid (HX531);
4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,f][1,4]oxazepin-11-yl]benzoic acid (HX620);
4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,f][1,4]thiazepin-11-yl]benzoic acid (HX630);
5-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl]-2-pyridinecarboxylic acid;
6-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl]-3-pyridinecarboxylic acid; and
4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,e]azepin-11-yl]benzoic acid (HX640), and lower alkyl esters of the above respective compounds, preferably methyl esters (for example, as to HX600, methyl 4-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl]benzoate).

[0020] Among the compounds of the present invention represented by the formula (II), examples of preferred compounds include, for example, those listed in the table set out below. In these compounds, R^1 is hydrogen atom or methyl group, Y is p-phenylene group, and X is -NR^7-. The abbreviation "Bzl" represents benzyl group, and indications such as 7-Me, 8-Et, 8-i-Pro, and 9-t-Bu represent that the compounds of formula (II) is substituted with methyl group at the 7-position, ethyl group at the 8-position, isopropyl group at the 8-position, and tert-butyl group at the 9-position, respectively. The indications such as 7-$(CH_2)_4$-8 and 7-$C(CH_3)_2CH_2CH_2C(CH_3)_2$-8 represent that the 7-position and the 8-position of the compounds of the formula (II) are bound with -$(CH_2)_4$- and -$C(CH_3)_2CH_2CH_2C(CH_3)_2$-, respectively.

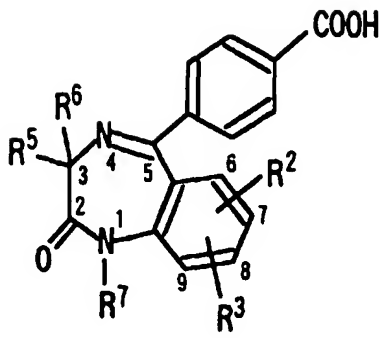


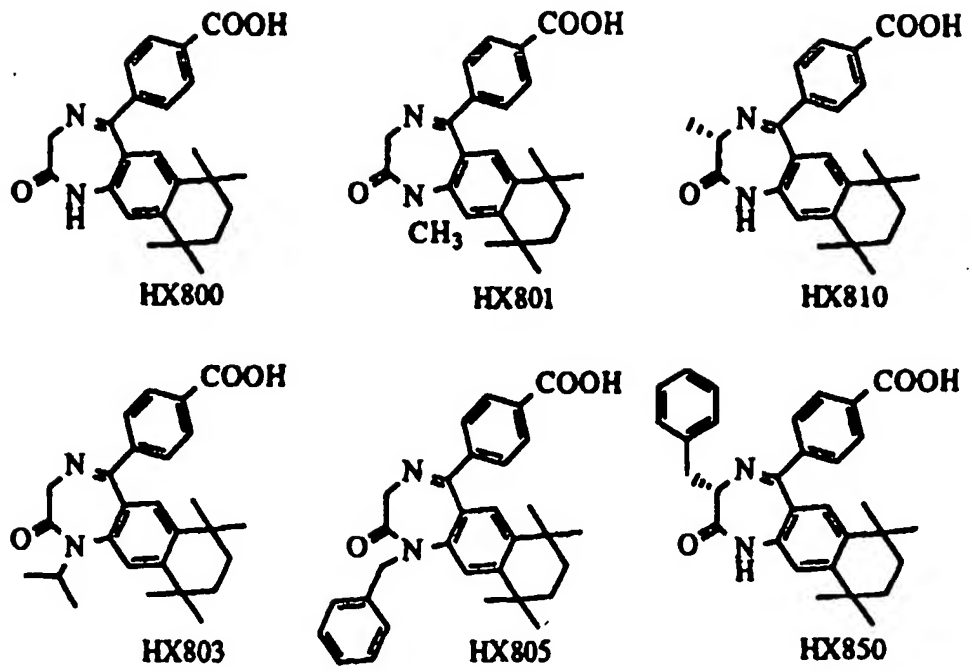
Table 1

R^2	R^3	R^5	R^6	R^7
H	H	H	H	H
7-Me	H	H	H	H
7-Me	8-Me	H	H	H
8-Me	9-Me	H	H	H
7-Et	8-Et	H	H	H
7-n-Pro	8-n-Pro	H	H	H
7-i-Pro	8-i-Pro	H	H	H
7-i-Pro	8-i-Pro	Me	H	H
7-i-Pro	8-i-Pro	Et	H	H
7-i-Pro	8-i-Pro	i-Pro	H	H
7-i-Pro	8-i-Pro	H	H	Me
7-i-Pro	8-i-Pro	Me	H	Me
7-i-Pro	8-i-Pro	Et	H	Me
7-i-Pro	8-i-Pro	Et	Me	Me
7-i-Pro	8-i-Pro	i-Pro	H	Me
7-i-Pro	8-i-Pro	i-Pro	H	i-Pro
7-i-Pro	8-n-Pro	H	H	H
7-t-Bu	8-t-Bu	Me	H	H

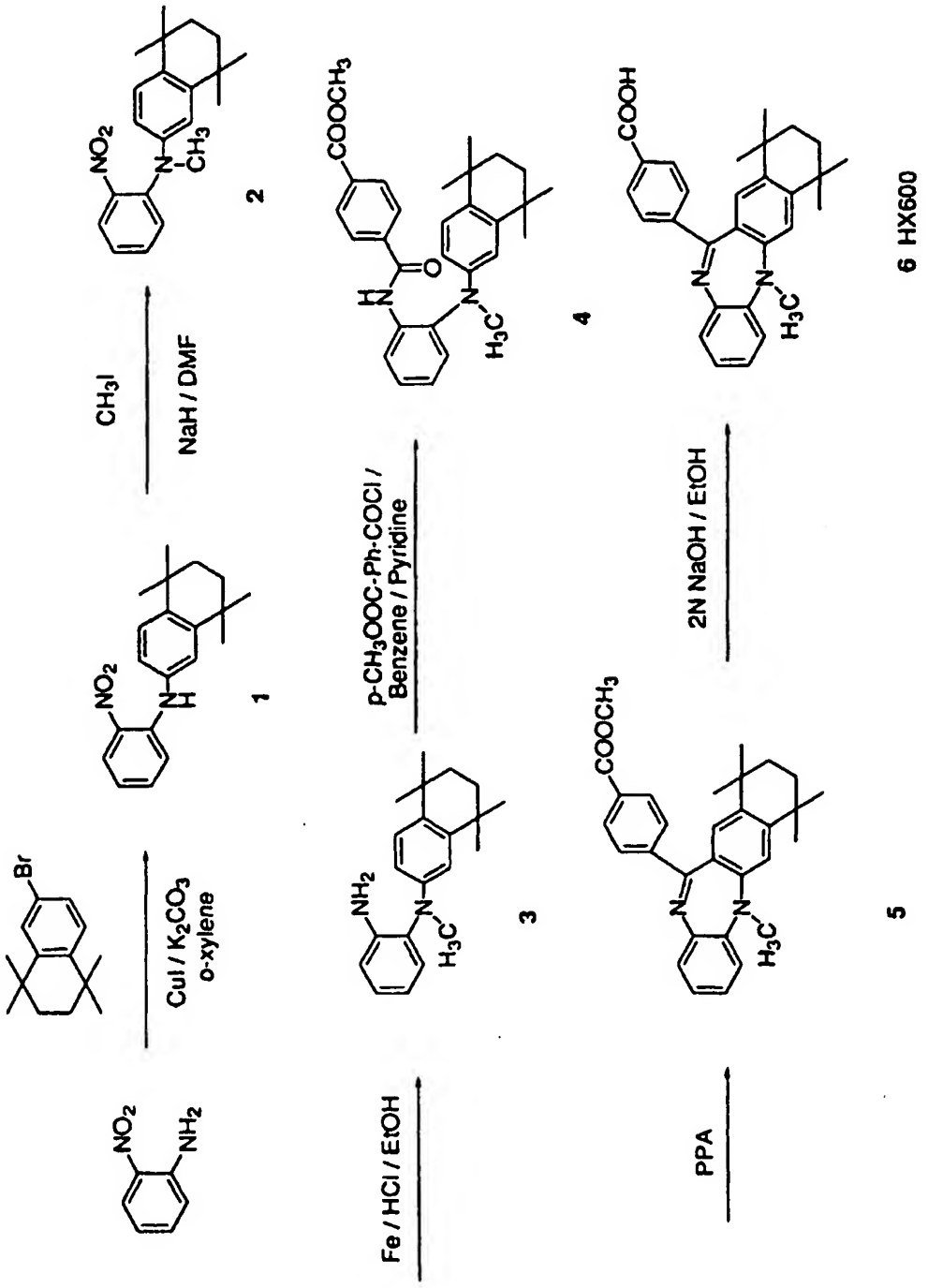
7-t-Bu	8-t-Bu	Et	H	H
7-t-Bu	8-t-Bu	i-Pro	H	H
7-t-Bu	8-t-Bu	H	H	Me
7-t-Bu	8-t-Bu	H	H	i-Pro
7-t-Bu	8-t-Bu	Me	H	Me
7-t-Bu	8-t-Bu	i-Pro	H	Me
7-t-Bu	8-t-Bu	Et	Me	Me
$7\text{-}(CH_2)_4\text{-}8$		H	H	H
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		H	H	H
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		Me	H	H
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		Me	Me	H
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		Me	Me	Me
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		Et	H	H
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		n-Pro	H	H
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		i-Pro	H	H
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		H	H	Me
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		H	H	i-Pro
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		n-Pro	H	Me
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		i-Pro	H	Me
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		i-Pro	H	i-Pro
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		t-Bu	H	H
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		t-Bu	H	Me
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		t-Bu	H	i-Pro
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		Bzl	H	H
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		Bzl	H	Me
$7\text{-}C(CH_3)_2CH_2CH_2C(CH_3)_2\text{-}8$		H	H	Bzl

[0021] Among them, examples of particularly preferred compounds include:

4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX800);
4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-1-methyl-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX801);
4-[3(S)-methyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX810);
4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-1-isopropyl-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX803);
4-[1-benzyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX805); and
4-[3(S)-benzyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX850), and lower alkyl esters of the above respective compounds, preferably, methyl esters (for example, as to HX800, methyl 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoate).



[0022] With reference to HX600, HX610, HX511, HX531 and HX545, as being preferred compounds that fall within the formula (I) of the present invention, exemplary manufacturing processes are shown in the schemes set out below. In addition, as for HX800, HX801 and HX850 being preferred compounds falling within the formula (II) of the present invention, exemplary preparing methods are shown in the same manners in the following schemes. However, the compounds of the present invention and the preparation methods thereof are not limited to those shown in the schemes. The preparing methods of the compounds of the present invention according to the schemes below are further detailed in the examples given in the specification. Therefore, it will be readily understood that any compounds falling within the scope of the present invention can be prepared by appropriately modifying or altering the starting materials, reagents, reaction conditions and the like disclosed in these exemplified methods.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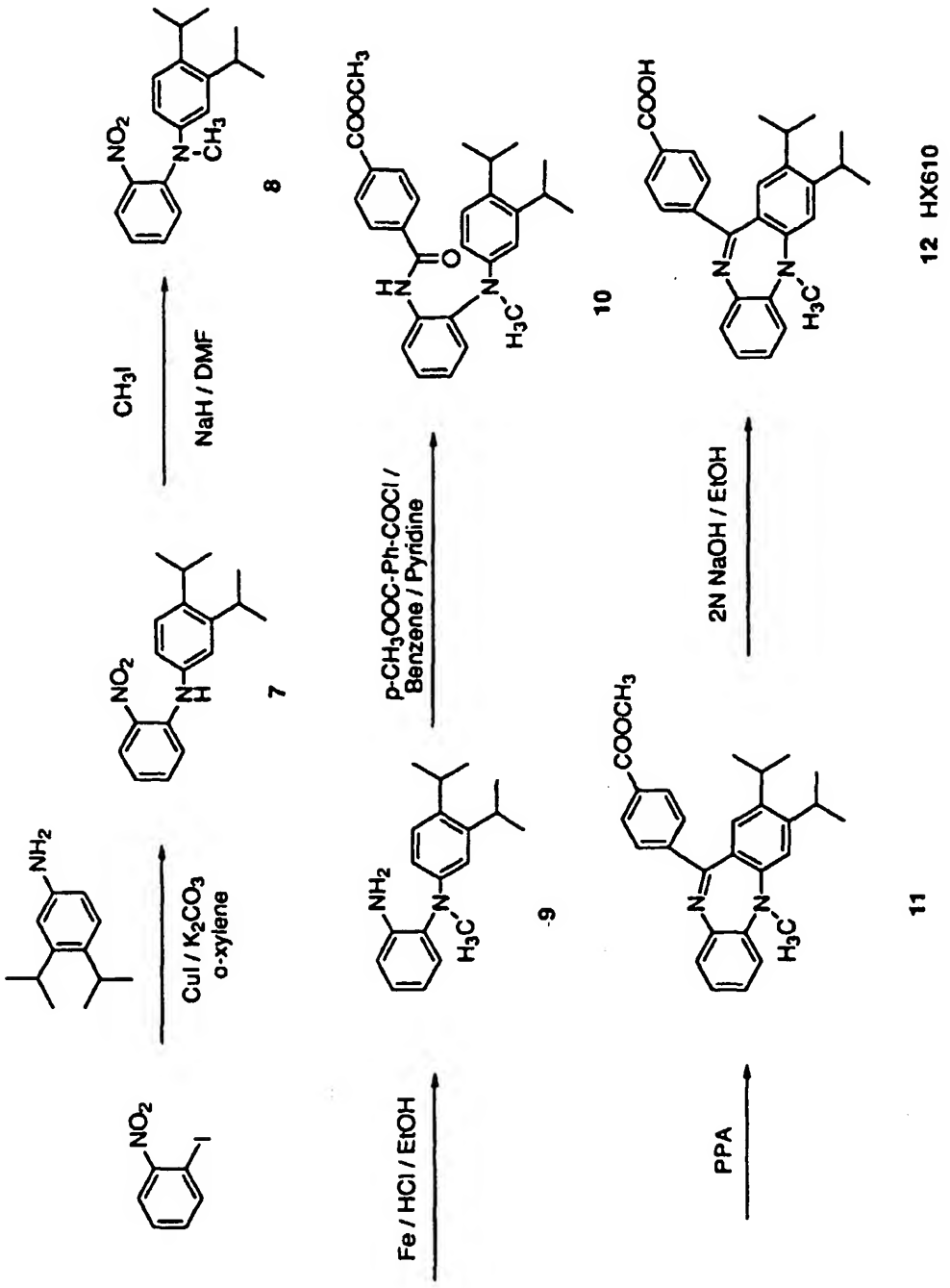
6 HX600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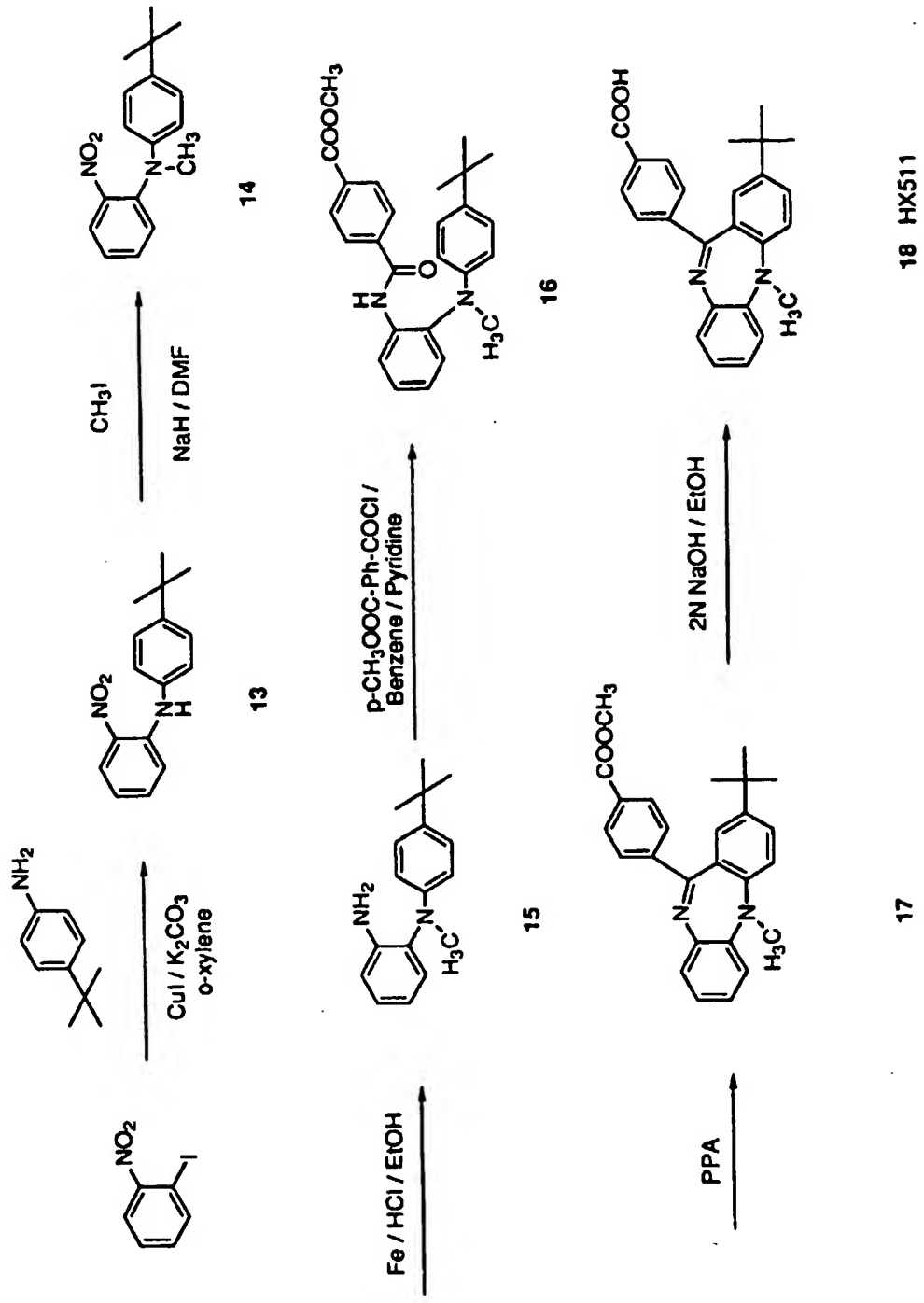
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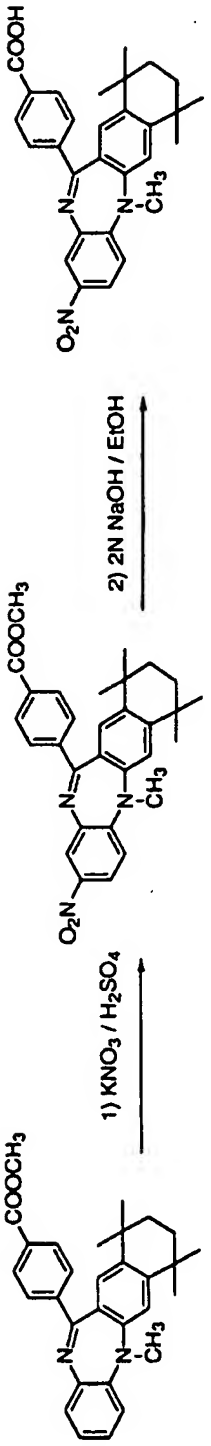
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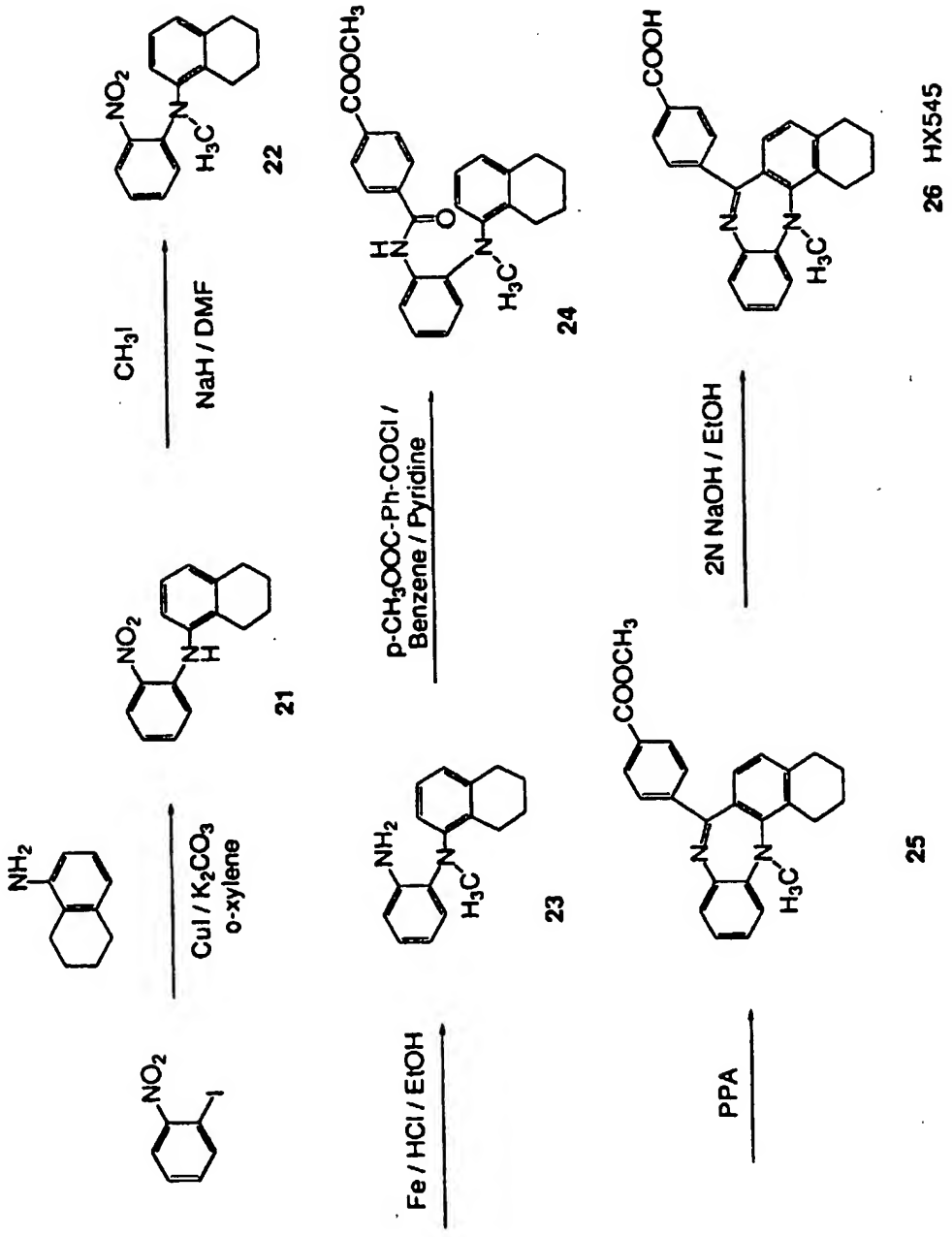
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26 HX545
2N NaOH / EtOH
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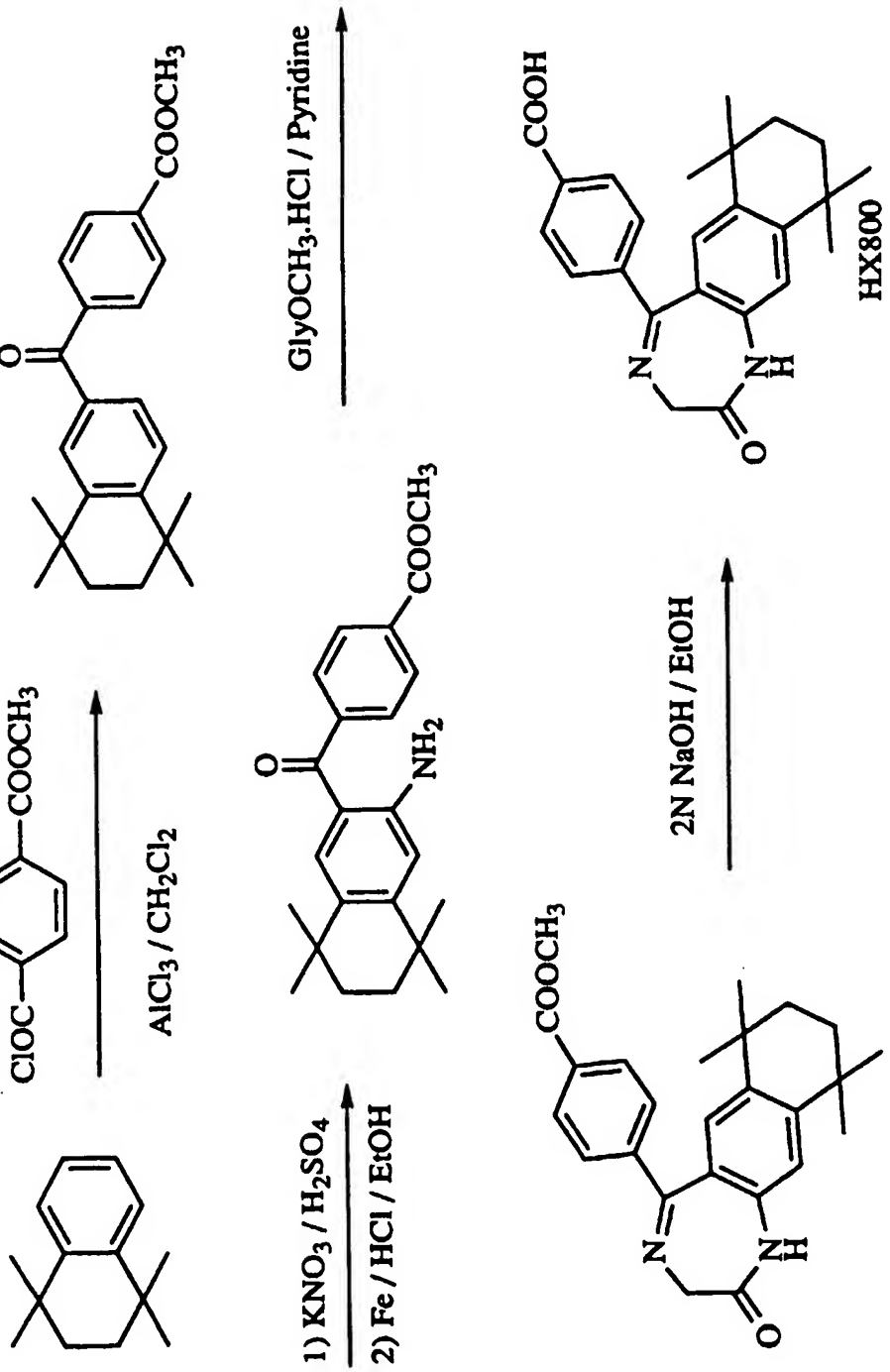
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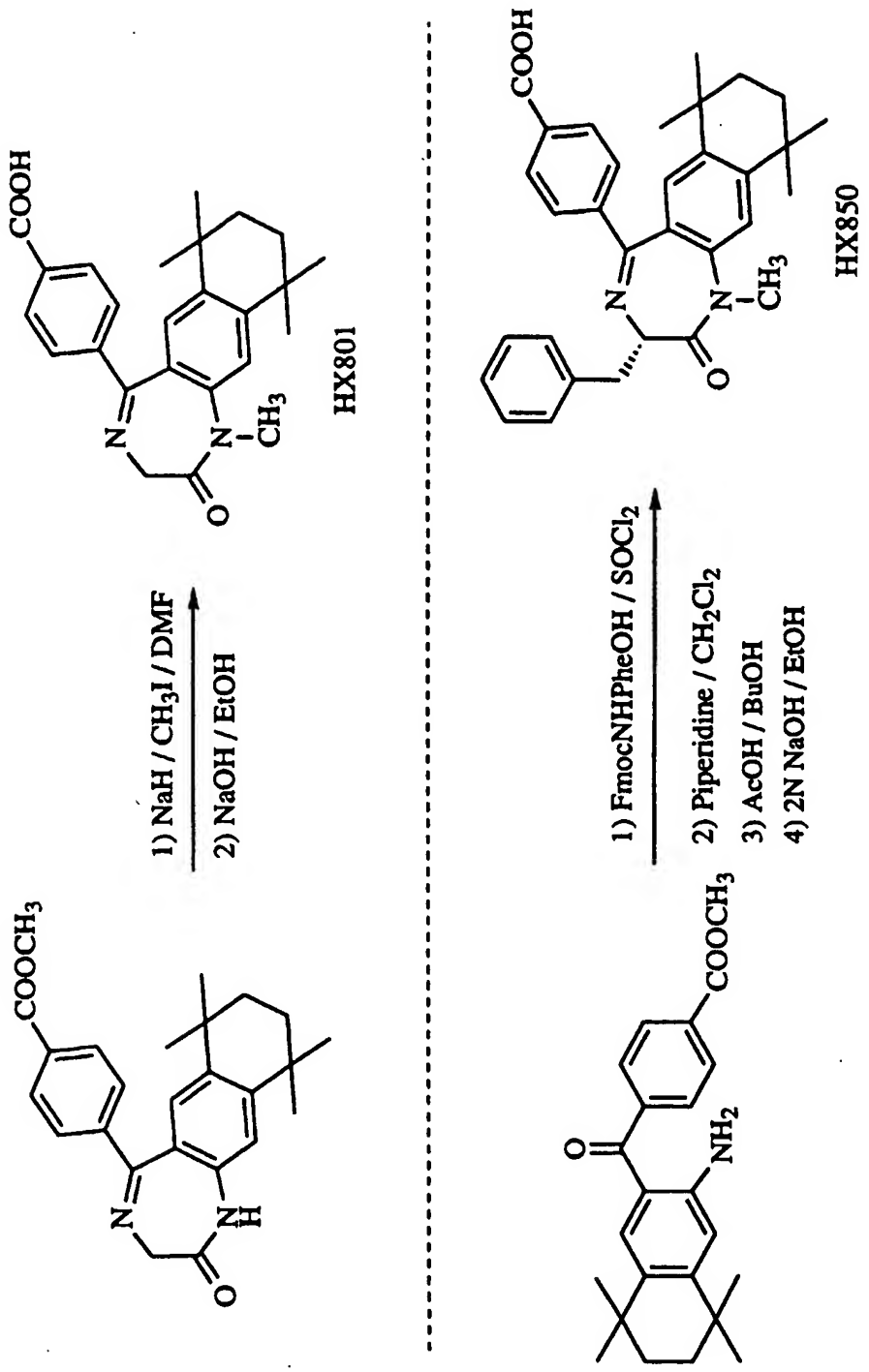


[0023] The compounds of the present invention, per se, have substantially no retinoid-like activity, or they have slight or moderate retinoid-like activities. However, where the compounds of the present invention are allowed to coexist with a retinoid such as retinoic acid, the physiological activities of the retinoid (typical examples include cell differentiation

activity, cell proliferation enhancing activity, life supporting activity and the like) are remarkably enhanced.

[0024] Although it is not intended to be bound by any specific theory, where a compound of the present invention has retinoid actions, synergistic actions are achieved. Therefore, where retinoic acid or the aforementioned compounds having the retinoic acid-like biological activities (for example, 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid: Am80) are administered as medicaments for the preventive or therapeutic treatments of vitamin A deficiency disease, hyperkeratosis of epithelial tissue, psoriasis, allergic diseases, immunological diseases such as rheumatism, bone diseases, leukemia, or cancers, the compounds of the present invention can be used as agents that enhance the activities of the retinoids.

[0025] Where the retinoids are not administered for the preventive and therapeutic treatments of the aforementioned diseases, the compounds of the present invention can enhance the activities of retinoic acid that inherently exists in living bodies, and thus the compounds of the present invention, per se, may be administered for the purpose of the preventive and therapeutic treatments of the aforementioned diseases. Furthermore, the compounds of the present invention may be used, in addition to the enhancement of the action of the retinoids, to enhance activities of physiologically active substances such as, for example, steroid compounds, vitamin D compounds such as vitamin D_3, thyroxine and the like that bind to receptors belonging to the intranuclear receptor super family existing in cellular nucleus to exert the physiological activities (Evans, R.M., Science, 240, p.889, 1988).

[0026] The compounds of the present invention, per se, may be administered as the medicaments comprising thereof. However, it is preferred that pharmaceutical compositions for oral administrations or parenteral administrations may be administered which can be prepared by methods well known to those skilled in the art. The compounds may be added to medicaments comprising a retinoid such as retinoic acid as an active ingredient, and used as pharmaceutical compositions in the form of so-called combined formulations. Examples of the pharmaceutical compositions suitable for oral administrations include, for example, tablets, capsules, powders, subtilized granules, granules, liquids, syrups and the like. Examples of the pharmaceutical compositions suitable for parenteral administrations include, for example, injections, suppositories, inhalants, eye drops, nasal drops, ointments, creams, patches and the like.

[0027] The aforementioned pharmaceutical compositions may be prepared by the addition of pharmacologically and pharmaceutically acceptable additives. Examples of pharmacologically and pharmaceutically acceptable additives include, for example, excipients, disintegrators and disintegrating aids, binders, lubricants, coating agents, colorants, diluents, base materials, dissolving agents and dissolving aids, isotonic agents, pH modifiers, stabilizers, propellants, adhesives and the like.

[0028] The doses of the medicament of the present invention are not particularly limited, and suitable doses can readily be suitably chosen for any types of administrations, for example, where the actions of a retinoid is enhanced by using the medicament of the present invention in combination with a medicament comprising a retinoid such as retinoic acid as an active ingredient, or where the medicament of the present invention is administered to enhance the actions of retinoic acid inherently exists in a living body without using a medicament comprising a retinoid in combination. For example, for oral administrations, the medicament may be used in a dose of 0.01-1,000 mg per day for an adult. Where the medicament of the present invention is used in combination with a medicament comprising a retinoid as an active ingredient, the medicament of the present invention can be administered in any periods of time, i.e., during the period of retinoid administration or before or after the period.

Examples

[0029] The present invention will be more specifically explained by referring to the following examples. However, the scope of the present invention is not limited to those examples. The compound numbers in the examples correspond to those in the schemes shown above.

Example 1: Preparation of 4-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl]benzoic acid (HX600)

[0030] Xylene (40 ml) was added to 6-bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (2.30 g, 8.61 mmol), o-nitroaniline (4.30 g, 31.2 mmol), K_2CO_3 (4.30 g, 31.2 mmol), and CuI (347 mg), and the mixture was heated under reflux for 24 hours. The xylene was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (AcOEt:n-hexane=1:50). The product was recrystallized from hexane to give Compound 1 (2.33 g, 84%).

^{1}H-NMR $CDCl_3$: 9.49 (s, 1H), 8.20 (dd, 1H, 8.4Hz, 1.5Hz), 7.33 (d, 2H, 8.4Hz), 7.20 (dd, 1H, 8.8Hz, 1.1Hz), 7.18 (d, 1H, 2.2Hz), 7.04 (dd, 1H, 8.4Hz, 2.2Hz), 6.73 (m, 1H), 1.71 (s, 4H), 1.30 (s, 6H), 1.28 (s, 6H)

[0031] NaH (60% in oil, 246 mg, 6.16 mmol, 1.5 eq) was washed with n- hexane and dried. Compound 1 (1.33 g, 4.10

mmol) dissolved in DMF (30 ml) was added to the base, and the mixture was stirred at room temperature for 30 minutes. This mixture was added with CH_3I (0.51 ml, 8.20 mmol) and stirred 3 hours. The reaction mixture was poured into ice water and extracted with dichloromethane, and the organic layer was washed with water and saturated brine and dried. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (AcOEt:n-hexane=1:40) to give Compound 2 (1.39 g, 100%).

^{1}H-NMR $CDCl_3$: 7.81 (dd, 1H, 8.1Hz, 1.5Hz), 7.53 (m, 1H), 7.34 (dd, 1H, 8.1Hz, 1.5Hz), 7.19 (m, 1H), 7.14 (d, 1H, 8.4Hz), 6.67 (d, 1H, 2.6Hz), 6.61 (dd, 1H, 8.4Hz, 2.6Hz), 3.29 (s, 3H), 1.63 (s, 4H), 1.23 (s, 6H), 1.18 (s, 6H)

[0032] Compound 2 (1.41 g, 4.17 mmol) was suspended in water (20 ml) and ethanol (40 ml), and added with concentrated hydrochloric acid (6.0 ml). The mixture was added with iron powder (2.2 g), and heated under reflux for 30 minutes. The reaction mixture was filtered to remove solid iron powder, and the filtrate was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and then dried. The solvent was evaporated under reduced pressure to give Compound 3 (1.25 g, 99%).

^{1}H-NMR $CDCl_3$: 7.11 (d, 1H, 8.8Hz), 7.06 (m, 2H), 6.81 (dd, 1H, 8.1Hz, 1.5Hz), 6.75 (m, 1H), 6.61 (d, 1H, 2.6Hz), 6.44 (dd, 1H, 8.4Hz, 2.6Hz), 3.82 (brs, 2H), 3.18 (s, 3H), 1.65 (s, 4H), 1.23 (s, 6H), 1.23 (s, 6H)

[0033] Compound 3 (1.25 g, 4.06 mmol) was dissolved in dried benzene (25 ml), and added with pyridine (0.5 ml). The mixture was added with terephthalic acid monomethyl ester chloride (966 mg, 4.87 mmol), and stirred at room temperature for 18 hours. The reaction mixture was added with ice water and diluted hydrochloric acid, and then extracted with ethyl acetate. The organic layer was dried, and the solvent was evaporated under reduced pressure to give a crude product (2.10 g). The product was purified by silica gel column chromatography (AcOEt:n-hexane=1:20) to give Compound 4 (1.72 g, 90%).

^{1}H-NMR $CDCl_3$: 8.57 (dd, 1H, 8.1Hz, 1.5Hz), 8.45 (s, 1H), 7.99 (d, 2H, 8.8Hz), 7.45 (d, 2H, 8.8Hz), 7.32 (m, 1H), 7.18-7.26 (m, 2H), 6.68 (d, 1H, 2.6Hz), 6.60 (dd, 1H, 8.4Hz, 2.6Hz), 3.93 (s, 3H), 3.31 (s, 3H), 1.64 (s, 4H), 1.24 (s, 6H), 1.16 (s, 6H)

[0034] Compound 4 (1.72 g, 3.65 mmol) was added with polyphosphoric acid (15.8 g), and stirred at 110°C for 2 hours and 40 minutes. The reaction mixture was added with water and then extracted with dichloromethane, and the organic layer was washed with saturated brine. The solvent was evaporated under reduced pressure, and the resulting residue was dried and then purified by silica gel column chromatography (AcOEt:n-hexane=1:30) to give the compound of the present invention (Compound 5: methyl 4-[5H-5-methyl-7,8-(2,5-dimethyl-2,5-hexano)dibenzo[b,e]diazepin-10-yl]benzoate (1.41 g, 86%). m.p. 238°C

^{1}H-NMR $CDCl_3$: 8.07 (d, 2H, 8.8Hz), 7.88 (d, 2H, 8.4Hz), 7.31 (dd, 1H, 7.7Hz, 1.8Hz), 7.15 (m, 1H), 7.09 (m, 1H), 6.98 (dd, 1H, 6.6Hz, 1.8Hz), 6.92 (s, 1H), 6.87 (s, 1H), 3.95 (s, 3H), 3.26 (s,3H), 1.63 (m, 4H), 1.32 (s, 3H), 1.26 (s, 3H), 1.12 (s, 3H), 1.04 (s, 3H)
Anal. Calc. for $C_{30}H_{32}N_2O_2$ C:79.61, H:7.13, N:6.19; Found C:79.56, H:7.27, N:6.12

[0035] Compound 5 (43 mg, 0.095 mmol) was suspended in ethanol (4 ml) and 2N NaOH (1.5 ml), and the suspension was stirred at room temperature for 1 hour and 10 minutes. The reaction mixture was adjusted to pH 2 using 2N HCl, and then extracted with dichloromethane. The organic layer was washed with water and saturated brine and dried, and the solvent was then evaporated under reduced pressure. The resulting residue was dried to give a compound of the present invention: HX600 (Compound 6, 37.1 mg, 89%). m.p. 282°C

^{1}H-NMR $CDCl_3$: 8.15 (d, 2H, 8.4Hz), 7.91 (d, 2H, 8.4Hz), 7.33 (dd, 1H, 7.7Hz, 1.5Hz), 7.15 (m, 1H), 7.09 (m, 1H), 6.98 (dd, 1H, 7.7Hz, 1.1Hz), 6.93 (s, 1H), 6.88 (s, 1H), 3.27 (s, 3H), 1.62 (m, 4H), 1.32 (s, 3H), 1.27 (s, 3H), 1.13 (s, 3H), 1.05 (s, 3H)
MS M^+ 438
Anal. Calc. for $C_{29}H_{30}N_2O_2$ C:79.42, H:6.89, N:6.39; Found C:79.12, H:7.15, N:6.25

Example 2: Preparation of 4-[5H-2,3-diisopropyl-5-methyldibenzo[b,e][1,4]diazepin-11-yl]benzoic acid (HX610)

[0036] 3,4-Diisopropylaniline (107 mg, 0.60 mmol), o-iodonitrobenzene (180 mg, 0.72 mmol), K_2CO_3 (83 mg, 0.60 mmol), and CuI (34 mg) were added to xylene (5 ml), and the mixture was heated under reflux for 18 hours. The xylene was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (AcOEt:n-

hexane = 1:50) to give Compound 7 (59 mg, 33%).

^{1}H-NMR $CDCl_3$: 9.50 (s, 1H), 8.20 (dd, 1H, 8.4Hz, 1.5Hz), 7.40 (m, 1H), 7.29 (d, 1H, 8.1Hz), 7.20 (dd, 1H, 8.8Hz, 1.1Hz), 7.13 (d, 1H, 2.2Hz), 7.08 (dd, 1H, 8.4Hz, 2.2Hz), 6.73 (m, 1H), 3.27 (m, 2H),1.25 (m, 12H)

[0037] NaH (60% in oil, 16 mg, 0.40 mmol, 2 eq) was washed with n-hexane, and dried. Compound 7 (58 mg, 0.20 mmol) dissolved in DMF (5 ml) was added to the base, and the mixture was stirred at room temperature for 30 minutes. The mixture was added with CH_3I (0.04 ml, 0.60 mmol), and then stirred for 3 hours. The reaction mixture was poured into ice water, and extracted with dichloromethane. The organic layer was washed with water and saturated brine. After dried, the solvent was evaporated under reduced pressure to give Compound 8 (57 mg, 93%).

^{1}H-NMR $CDCl_3$: 7.81 (dd, 1H, 8.1Hz, 1.5Hz), 7.53 (m, 1H), 7.34 (dd, 1H, 8.1Hz, 1.5Hz), 7.18 (m, 1H), 7.10 (d, 1H, 9.2Hz), 6.62 (m, 2H), 3.31 (s, 3H), 3.17 (septet, 2H), 1.19 (d, 6H, 7.0Hz), 1.14 (d, 6H, 7.0Hz)

[0038] Compound 8 (52.5 mg, 0.17 mmol) was suspended in water (2 ml) and ethanol (4 ml), and added with concentrated hydrochloric acid (0.5 ml). The mixture was added with iron powder (200 mg), and heated under reflux for 30 minutes. The reaction mixture was filtered to remove solid iron powder, and the filtrate was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried, and the solvent was then evaporated under reduced pressure to give Compound 9 (40.0 mg, 84%).

^{1}H-NMR $CDCl_3$: 7.07 (m, 3H), 6.82 (dd, 1H, 7.7Hz, 1.5Hz), 6.76 (m, 1H), 6.59 (d, 1H, 2.9Hz), 6.46 (dd, 1H, 8.4Hz, 2.6Hz), 3.84 (brs, 2H), 3.20 (s, 3H), 3.18 (m, 2H), 1.19 (m, 12H)

[0039] Compound 9 (39 mg, 0.14 mmol) was dissolved in dry benzene (5 ml), and added with pyridine (0.1 ml). The mixture was added with terephthalic acid monomethyl ester chloride (36 mg, 0.18 mmol), and stirred at room temperature for 3 hours. The reaction mixture was added with ice water and diluted hydrochloric acid, and then extracted with ethyl acetate. The organic layer was dried, and the solvent was evaporated to give a crude product (67.3 mg). The product was purified by silica gel column chromatography (AcOEt:n-hexane = 1:20) to give Compound 10 (44.4 mg, 71%).

^{1}H-NMR $CDCl_3$: 8.58 (d, 1H, 9.5Hz), 8.47 (m, 1H), 7.98 (d, 2H, 8.4Hz), 7.46 (d, 2H, 8.4Hz), 7.32 (m, 1H), 7.22 (m, 2H), 7.15 (d, 1H, 8.4Hz), 6.66 (d, 1H, 2.9Hz), 6.60 (dd, 1H, 8.4Hz 2.6Hz), 3.93 (s, 3H), 3.31 (s, 3H), 3.21 (septet, 2H), 1.20 (d, 6H, 6.6Hz), 1.13 (d, 6H, 7.0Hz)

[0040] Compound 10 (44 mg, 0.10 mmol) was added with polyphosphoric acid (1.2 g), and stirred at 120°C for 1 hour. The reaction mixture was added with water, and extracted with dichloromethane. The organic layer was washed with saturated brine and dried, and the solvent was then evaporated under reduced pressure. The resulting residue was dried, and then purified by silica gel column chromatography (AcOEt:n-hexane=1:30) to give a compound of the present invention (Compound 11: methyl 4-[5H-5-methyl-7,8-diisopropyldibenzo[b,e]diazepin-10-yl]benzoate) (19.2 mg, 45%).

^{1}H-NMR $CDCl_3$: 8.07 (d, 2H, 8.8Hz), 7.87 (d, 2H, 8.4Hz), 7.31 (dd, 1H, 7.7Hz, 1.8Hz), 7.15 (m, 1H), 7.08 (m, 1H), 6.98 (m, 1H), 6.99 (s, 1H), 6.97 (s, 1H), 3.95 (s, 3H), 3.27 (s, 3H), 3.23 (m, 1H), 3.13 (m, 1H), 1.28 (d, 3H, 6.6Hz), 1.26 (d, 3H, 7.0Hz), 1.08 (d, 3H, 7.0Hz), 1.01 (d, 3H, 7.0Hz)

[0041] Compound 11 (18 mg, 0.043 mmol) was suspended in ethanol (2 ml) and 2N NaOH (1 ml), and stirred at room temperature for 40 minutes. The reaction mixture was adjusted to pH 2 using 2N HCl, and extracted with dichloromethane. The organic layer was washed with water and saturated brine, and the solvent was then evaporated under reduced pressure. The resulting residue was dried to give a compound of the present invention: HX610 (Compound 12, 15.6 mg, 88%). The product was recrystallized from a mixture of ethanol/water to give 10.5 mg of purified compound. m.p. 263°C

^{1}H-NMR $CDCl_3$: 8.14 (d, 2H, 8.8Hz), 7.91 (d, 2H, 8.4Hz), 7.32 (dd, 1H, 7.7Hz, 1.8Hz), 7.16 (m, 1H), 7.10 (m, 1H), 6.99 (dd, 1H, 8.1Hz, 1.1Hz), 6.90 (s, 1H), 6.83 (s, 1H), 3.28 (s, 3H), 3.24 (m, 1H), 3,14 (m, 1H), 1.28 (d, 3H, 7.0Hz), 1.23 (d, 3H, 6.6Hz), 1.10 (d, 3H, 7.0Hz), 1.02 (d, 3H, 7.0Hz)
Anal. Calc. for $C_{27}H_{28}N_2O_2$ C:78.61, H:6.84, N:6.79; Found C:78.36, H:6.92, N:6.67

Example 3: Preparation of 4-[5H-2-tert-butyl-5-methyldibenzo[b,e][1,4]diazepin-11-yl]benzoic acid (HX511)

[0042] 4-tert-Butylaniline (761 mg, 5.1 mmol), K_2CO_3 (697, 5.1 mmol), CuI 95 mg, and o-xylene (10 ml) were added to o-iodonitrobenzene (1.25 g, 5.0 mmol), and the mixture was stirred at 150°C for 11 hours. The reaction mixture was

purified by silica gel column chromatography (AcOEt:n-hexane=1:40) to give Compound 13 (529.1 mg, 39%).

^{1}H-NMR $CDCl_3$: 9.48 (s, 1H), 8.20 (dd, 1H, 8.4Hz, 1.5Hz), 7.43 (d, 2H, 8.8Hz), 7.35 (m, 1H), 7.22 (m, 3H), 6.76 (m, 1H), 1.35 (s, 9H)

[0043] NaH (60% in oil, 73 mg, 1.82 mmol) was washed with hexane, and dried. DMF (1 ml) was added to the NaH, and the resulting suspension was added with Compound 13 (241.7 mg, 0.895 mmol) dissolved in DMF (5 ml). The reaction mixture was stirred at room temperature for 20 minutes, added with methyl iodide (0.18 ml, 2.78 mmol, 3 eq), and stirred for 3 hours. The reaction mixture was poured into ice water, and extracted with dichloromethane. The organic layer was washed with water and saturated brine and dried, and then concentrated under reduced pressure to give Compound 14 (245.3 mg, 97%).

^{1}H-NMR $CDCl_3$: 7.83 (dd, 1H, 8.1Hz, 1.5Hz), 7.57 (m, 1H), 7.36 (dd, 1H, 8.1Hz, 1.5Hz), 7.22 (d, 2H, 8.8Hz), 6.70 (d, 2H, 9.2Hz), 3.29 (s, 3H), 1.27 (s, 9H)

[0044] Water (4 ml), ethanol (8 ml), and iron powder (406 mg), and then concentrated hydrochloric acid (1.0 ml) were added to Compound 14 (240 mg, 0.845 mmol), and the mixture was heated under reflux for 20 minutes. The reaction mixture was added with ethyl acetate, and filtered. The filtrate was washed with water and saturated brine. The organic layer was dried and concentrated under reduced pressure to give Compound 15 (184.6 mg, 86%).

^{1}H-NMR $CDCl_3$: 7.22 (d, 2H, 8.8Hz), 7.08 (m, 1H), 7.04 (dd, 1H, 8.1Hz, 1.5Hz), 6.82 (dd, 1H, 7.7Hz, 1.5Hz), 6.77 (m, 1H), 6.61 (d, 2H, 8.8Hz), 3.83 (brs, 2H), 3.20 (s, 3H), 1.28 (s, 9H)

[0045] Compound 15 (174 mg, 0.685 mmol) was dissolved in dry benzene (7 ml), and added with pyridine (0.1 ml, 1.25 mmol). The mixture was added with terephthalic acid monomethyl ester chloride (163 mg, 0.823 mmol), and stirred at room temperature for 2 hours and 15 minutes. The reaction mixture was added with ice water and diluted hydrochloric acid, and then extracted with ethyl acetate. The organic layer was dried, and the solvent was evaporated under reduced pressure to give a crude product (320.1 mg). This product was purified by silica gel column chromatography (AcOEt:n-hexane=1:20) to give Compound 16 (206.7 mg, 73%).

^{1}H-NMR $CDCl_3$: 8.60 (d, 1H, 7.0Hz), 8.57 (s, 1H), 8.00 (d, 2H, 8.4Hz), 7.53 (d, 2H, 8.4Hz), 7.33 (m, 1H), 7.28 (d, 2H, 8.8Hz), 7.21 (m, 2H), 6.72 (d, 2H, 8.8Hz), 3.93 (s, 3H), 3.28 (s, 3H), 1.29 (s, 9H)

[0046] Compound 16 (202.6 mg, 0.487 mmol) was added with polyphosphoric acid (2.5 g), and the mixture was stirred at 130°C for 2 hours. Additional polyphosphoric acid (2.0 g) was added, and stirring was continued for 1 hour. The reaction mixture was added with water, and extracted with dichloromethane. The organic layer was concentrated and dried to give a crude product (164.9 mg). This crude product was purified by silica gel column chromatography (AcOEt:n-hexane=1:40 → 1:20), and the resulting purified product was further purified by silica gel column chromatography (AcOEt:n-hexane=1:20) to give Compound 17 (22.0 mg, 11%).

^{1}H-NMR $CDCl_3$: 8.08 (d, 2H, 8.4Hz), 7.86 (d, 2H, 8.4Hz), 7.42 (dd, 1H, 8.4Hz, 2.2Hz), 7.32 (dd, 1H, 7.7Hz, 1.8Hz), 7.15 (m, 1H), 7.09 (m, 1H), 6.98 (m, 3H), 3.95 (s, 3H), 3.26 (s, 3H), 1.18 (s, 9H)

[0047] Compound 17 (20.1 mg, 0.05 mmol) was added with 2N NaOH (1.0 ml) and ethanol (2.0 ml), and the mixture was stirred for 3 hours and 15 minutes. The reaction mixture was acidified by adding 2N hydrochloric acid, and extracted with dichloromethane. The organic layer was washed with water and saturated brine and dried, and the solvent was then concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (dichloromethane:methanol=20:1) to give the compound of the present invention: HX511 (Compound 18, 16.5 mg, 85%). The product was recrystallized from a mixture of ethanol/water to give purified compound. m.p. 249°C

^{1}H-NMR $CDCl_3$: 8.14 (d, 2H, 8.4Hz), 7.90 (d, 2H, 8.4Hz), 7.43 (dd, 1H, 8.4Hz, 2.2Hz), 7.32 (dd, 1H, 7.7Hz, 1.8Hz), 7.15 (m, 1H), 7.09 (m, 1H), 6.98 (m, 3H), 3.26 (s, 3H), 1.19 (s, 9H)
Anal. Calc. for $C_{25}H_{24}N_2O_2$ C:78.10, H:6.29, N:7.29; Found C:77.92, H:6.40, N:7.13

Example 4: Preparation of 4-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyl-8-nitrodibenzo[b,e][1,4]diazepin-11-yl]benzoic acid (HX531)

[0048] Compound 5 (methyl ester of HX600, 102 mg, 0.226 mmol) was dissolved in concentrated sulfuric acid (5 ml),

and the solution was added with KNO_3 (36.5 mg, 0.36 mmol) under ice cooling. After 1 hour, the reaction mixture was poured into ice water, and extracted with dichloromethane. The organic layer was washed with saturated aqueous sodium hydrogencarbonate, water, and brine successively and dried, and the solvent was then evaporated under reduced pressure to give a crude product (102 mg). This crude product was purified by silica gel column chromatography (AcOEt:n-hexane=1:20) to give Compound 19 (19.3 mg, 17%).

^{1}H-NMR $CDCl_3$: 8.14 (d, 1H, 2.6Hz), 8.11 (d, 2H, 8.8Hz), 8.01 (dd, 1H, 8.8Hz, 2.6Hz), 7.89 (d, 1H, 8.8Hz), 6.93 (s, 1H), 6.91 (s, 1H), 3.97 (s, 3H), 3.32 (s, 3H), 1.66 (m, 4H), 1.32 (s, 3H), 1.28 (s, 3H), 1.14 (s, 3H), 1.07 (s, 3H)

[0049] Compound 19 (17.3 mg, 0.035 mmol) was added with 2N NaOH (1.0 ml) and ethanol (2.0 ml), and the mixture was stirred at room temperature for 90 minutes. The reaction mixture was acidified with 2N HCl, and extracted with dichloromethane. The organic layer was washed with water and saturated brine and dried, and the solvent was then evaporated under reduced pressure to give a compound of the present invention: HX531 (Compound 20, 15.0 mg, 89%). The product was recrystallized from a mixture of ethanol/water to give purified compound. m.p. >300°C

^{1}H-NMR $CDCl_3$: 8.15 (m, 3H), 8.01 (dd, 1H, 8.8Hz, 2.6Hz), 7.90 (d, 2H, 7.3Hz), 7.00 (d, 1H, 9.2Hz), 6.93 (s, 1H), 6.92 (s, 1H), 3.31 (s, 3H), 1.65 (m, 4H), 1.32 (s, 3H), 1.27 (s, 3H), 1.14 (s, 3H), 1.07 (s, 3H)
Anal. Calc. for $C_{29}H_{29}N_3O_4$ C:72.03, H:6.04, N:8.69; Found C:71.89, H:6.25, N:8.54

Example 5: Preparation of 4-[5H-3,4-(1,4-butano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl]benzoic acid (HX545)

[0050] Xylene (40 ml) was added to 5,6,7,8-tetrahydro-1-naphthylamine (1.83 g, 12.43 mmol), o-iodonitrobenzene (3.1 g, 12.43 mmol), K_2CO_3 (1.72 g, 12.43 mmol), and CuI (217 mg), and the mixture was heated under reflux for 18 hours. Then, the xylene was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (AcOEt:n-hexane =1:50) to give Compound 21. (736 mg, 22%).

^{1}H-NMR $CDCl_3$: 9.30 (s, 1H), 8.20 (dd, 1H, 8.8Hz, 1.5Hz), 7.32 (m, 1H), 7.15 (m, 2H), 7.04 (d, 1H, 7.3Hz), 6.90 (dd, 1H, 8.4Hz, 1.1Hz), 6.72 (m, 1H), 2.83 (m, 2H), 2.64 (m, 2H), 1.79 (m, 4H)

[0051] NaH (60% in oil, 114 mg, 2.84 mmol, 2 eq) was washed with hexane and dried. Compound 21 (381 mg, 1.42 mmol) dissolved in DMF (8 ml) was added to the base, and the mixture was stirred at room temperature for 15 minutes. This mixture was added with methyl iodide (0.37 ml, 5.68 mmol), and stirred for 3 hours and 30 minutes. The reaction mixture was poured into ice water, and extracted with dichloromethane. The organic layer was dried, and the solvent was then evaporated under reduced pressure to give a crude product. This crude product was purified by silica gel column chromatography (AcOEt:n-hexane=1:100), and the resulting compound was washed with water and saturated brine. After dried, the solvent was evaporated to give Compound 22 (293 mg, 73%).

^{1}H-NMR $CDCl_3$: 7.67 (dd, 1H, 8.1Hz, 1.8Hz), 7.34 (m, 1H), 7.08 (t, 1H, 7.7Hz), 6.97 (d, 1H, 7.3Hz), 6.86 (m, 3H), 3.16 (s, 3H), 2.81 (m, 2H), 2.57 (m, 2H), 1.76 (m, 4H)

[0052] Compound 22 (101.6 mg, 0.36 mmol) was suspended in a mixture of water (2 ml) and ethanol (6 ml), and added with concentrated hydrochloric acid (0.5 ml). The mixture was added with iron powder (201 mg), and heated under reflux for 10 minutes. The reaction mixture was filtered to remove solid materials, and the filtrate was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried, and then the solvent was evaporated under reduced pressure to give Compound 23 (81.1 mg, 89%).

^{1}H-NMR $CDCl_3$: 7.13 (t, 1H, 7.7Hz), 7.03 (d, 1H, 7.3Hz), 6.93 (m, 1H), 6.83 (d, 1H, 7.0Hz), 6.75 (dd, 1H, 7.7Hz, 1.1Hz), 6.64 (m, 2H), 3.96 (brs, 2H), 3.05 (s, 3H), 2.76 (m, 2H), 2.15 (m, 2H), 1.65 (m, 4H)

[0053] Compound 23 (81 mg, 0.32 mmol) was dissolved in dry benzene (5 ml), and the solution was added with pyridine (0.1 ml). The solution was added with terephthalic acid monomethyl ester chloride (79.6 mg, 0.40 mmol), and stirred at room temperature for 16 hours. The reaction mixture was added with ice water and diluted hydrochloric acid, and then extracted with ethyl acetate. The organic layer was dried, and the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt:n-hexane=1:20 → 1:10) to give Compound 24 (113.9 mg, 86%)

^{1}H-NMR $CDCl_3$: 8.45 (s, 1H), 8.36 (d, 1H, 7.7Hz), 8.09 (d, 2H, 8.1Hz), 7.68 (d, 2H, 8.4Hz), 7.13 (m, 3H), 6.99 (dd, 1H, 8.1Hz, 1.5Hz), 6.96 (d, 1H, 7.3Hz), 6.91 (d, 1H, 7.7Hz), 3.96 (s, 3H), 3.10 (s, 3H), 2.73 (m, 2H), 2.31 (m, 2H),

1.60 (m, 2H), 1.51 (m, 2H)

[0054] Polyphosphoric acid (1.83 g) was added to Compound 24 (113 mg, 0.273 mmol), and the mixture was stirred at 130°C for 1 hour. The reaction mixture was added with water and then extracted with dichloromethane, and the organic layer was washed with saturated brine. Alter dried, the solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (AcOEt:n-hexane=1:40 → 1:20) to give Compound 25 (67.9 mg, 63%).

^{1}H-NMR $CDCl_3$: 8.10 (d, 2H, 8.8Hz), 7.91 (d, 2H, 8.4Hz), 7.40 (dd, 1H, 8.1Hz, 2.2Hz), 7.25 (m, 1H), 7.20 (m, 2H), 6.89 (d, 1H, 8.1Hz), 6.82 (d, 1H, 8.1Hz), 3.95 (s, 3H), 3.06 (s, 3H), 3.02 (m, 2H), 2.78 (m, 2H), 1.95 (m, 1H), 1.85 (m, 1H), 1.75 (m, 2H)

[0055] 2N NaOH (2.0 ml) and ethanol (5.0 ml) were added to Compound 25 (66.3 mg, 0.167 mmol), and the mixture was stirred at room temperature for 1 hour and 15 minutes. The reaction mixture was acidified with 2N HCl, and extracted with dichloromethane. The organic layer was washed with water and saturated brine and dried, and the solvent was then evaporated under reduced pressure to give a compound of the present invention: HX545 (Compound 26, 60.7 mg, 95%). The product was recrystallized from a mixture of ethanol/water to give purified compound. m.p. 273°C

^{1}H-NMR $CDCl_3$: 8.17 (d, 2H, 8.8.Hz), 7.95 (d, 2H, 8.4Hz), 7.42 (dd, 1H, 7.7Hz, 1.8Hz), 7.22 (m, 3H), 6.91 (d, 1H, 8.1Hz), 6.83 (d, 1H, 8.1Hz), 3.07 (s, 3H), 3.02 (m, 2H), 2.80 (m, 2H), 1.95 (m, 2H), 1.84 (m, 2H), 1.75 (m, 4H)
Anal. Calc. for $C_{25}H_{22}N_2O_2$ C:78.51, H:5.80, N:7.32; Found C:78.32, H:5.83, N:7.13

Example 6: Preparation of 4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,f][1,4]oxazepine-11-yl]benzoic acid (HX620)

[0056] DMSO (5 ml) was added to 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthol (97 mg, 0.475 mmol), o-chloronitrobenzene (77 mg, 0.48 mmol) and potassium hydroxide (27 mg, 0.48 mmol), and stirred at 90°C for 17 hours and 30 minutes. To the reaction mixture, water, dichloromethane and concentrated hydrochloric acid (1 ml) were added, and the organic layer was washed with diluted hydrochloric acid and brine. After dried, the solvent was evaporated under reduced pressure to give a crude product (139.7 mg). This crude product was purified by silica gel column chromatography (AcOEt:n-hexane=1:30) to give o-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-nitrophenol (Compound 27, 103.1 mg, 67%, colorless oil)

^{1}H-NMR $CDCl_3$: 7.93 (dd, 1H, 8.1Hz, 1.5Hz), 7.46 (m, 1H), 7.29 (d, 1H, 8.8Hz), 7.14 (m, 1H), 7.01 (d, 1H, 2.6Hz), 6.99 (dd, 1H, 8.4Hz, 1.1Hz), 6.80 (dd, 1H, 8.4Hz, 2.6Hz), 1.69 (s, 4H), 1.28 (s,6H), 1.25 (s, 6H)

[0057] Compound 27 was suspended in water (2 ml) and ethanol (6 ml), and added with concentrated hydrochloric acid (0.5 ml). To this mixture, iron powder (220 mg) was added, and heated under reflux for 30 minutes. The reaction mixture was filtered to remove solid matter, and the filtrate was extracted with ethyl acetate. The organic layer was washed with water and saturated brine. After dried, the solvent was evaporated under reduced pressure to give o-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-aminophenol (Compound 28, 80.5 mg, 85%).

^{1}H-NMR $CDCl_3$: 7.21 (d, 1H, 8.8Hz), 6.97 (d, 1H, 2.9Hz), 6.95 (m, 1H), 6.85 (dd, 1H, 8.1Hz, 1.5Hz), 6.82 (dd, 1H, 7.7Hz, 1.5Hz), 6.70 (m, 2H), 3.82 (brs, 2H), 1.68 (s, 4H), 1.26 (s, 6H), 1.25 (s, 6H)

[0058] Compound 28 (80.5 mg, 0.264 mmol) was dissolved in dried benzene (5 ml), and added with pyridine (0.1 ml, 1.25 mmol). Terephthalic acid monomethyl ester chloride (63 mg, 0.317 mmol) was added to this solution, and stirred at room temperature for 16 hours and 30 minutes. The reaction mixture was added with ice water and diluted hydrochloric acid, and extracted with ethyl acetate. After dried, the solvent was evaporated under reduced pressure to give a crude product (133 mg). This crude product was purified by silica gel column chromatography (AcOEt:n-hexane=1:20 → 1:2) to give methyl 4-[2-(o-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalenyl)amino)carbamoyl]benzoate (Compound 29, 115.8 mg, 94%).

^{1}H-NMR $CDCl_3$: 8.59 (dd, 1H, 8.1Hz, 1.5Hz), 8.56 (brs, 1H), 8.11 (d, 2H, 8.8Hz), 7.86 (d 2H, 8.4Hz), 7.30 (d, 1H, 8.8Hz), 7.16 (m, 1H), 7.07 (dd, 1H, 8.1H, 1.5Hz), 7.04 (d, 1H, 2.6Hz), 6.90 (dd, 1H, 8.1Hz, 1.5Hz), 6.81 (dd, 1H, 8.4Hz, 2.6Hz), 3.95 (s, 3H), 1.70 (s, 4H), 1.28 (s, 6H), 1.25 (s, 6H)

[0059] Polyphosphoric acid (2.2 g) was added to Compound 29 (111 mg, 0.238 mmol), and stirred at 100°C for 1 hour and 30 minutes. The reaction mixture was added with water, and extracted with dichloromethane. After the organic layer

was dried, the solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (AcOEt:n-hexane =1:40) to give methyl 4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,f][1,4]oxazepin-11-yl]benzoate (Compound 30, 33.4 mg, 31%).

^{1}H-NMR $CDCl_3$: 8.12 (d, 2H, 8.4Hz), 7.92 (d, 2H, 8.8Hz), 7.44 (m, 1H), 7.21 (m, 3H), 7.16 (s, 1H), 7.01 (s, 1H), 1.66 (m, 4H), 1.30 (s, 6H), 1.11 (s, 6H)

[0060] Compound 30 (30.0 mg, 0.067 mmol) was suspended in ethanol (5 ml) and 2N sodium hydroxide (1 ml), and stirred at room temperature for 40 minutes. The reaction mixture was acidified with 2N hydrochloric acid, and extracted with dichloromethane. The organic layer was washed with water and saturated brine. After dried, the solvent was evaporated under reduced pressure to give a compound of the present invention, 4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,f][1,4]oxazepin-11-yl-benzoic acid (HX620: Compound 31, 29.0 mg, 100%). The product was recrystallized from a mixture of ethanol/water to give purified compound. m.p. 289 °C

^{1}H-NMR $CDCl_3$: 8.19 (d, 2H, 8.8Hz), 7.97 (d, 2H, 8.8Hz), 7.46 (m, 1H), 7.22 (m, 3H), 7.18 (s, 1H), 7.02 (s, 1H), 1.66 (s, 4H), 1.31 (s, 6H), 1.12 (s, 6H)

Example 7: Preparation of 4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,f][1,4]thiazepine-11-yl]benzoic acid (HX630)

[0061] 1,2,3,4-Tetrahydro-1,1,4,4-tetramethylnaphthalene (6.0 g, 32.0 mmol) was added to chlorosulfonic acid (10 ml) at 0°C, and stirred for 1 hour. The reaction mixture was poured into ice water, and extracted with ethyl acetate. The organic layer was washed with saturated brine and, alter dried, the solvent was evaporated under reduced pressure. The residue was added with zinc powder (10 g, 15.2 mmol) and ethanol (20 ml), then added with concentrated hydrochloric acid (40 ml) over 5 minutes, and heated under reflux for 1 hour and 25 minutes. The reaction mixture was extracted by adding ice water and ethyl acetate, and the organic layer was washed with saturated brine. After dried, the solvent was evaporated under reduced pressure to give a crude product (6.82 g).

^{1}H-NMR $CDCl_3$: 3.37 (s, 1H, -SH)

[0062] DMSO (8 ml) was added to the above crude thiophenol compound (290 mg, 1.3 mmol), o-chloronitrobenzene (212 mg, 1.3 mmol) and potassium hydroxide (71.5 mg, 1.3 mmol), and stirred at 100°C for 15 hours and 40 minutes. The reaction mixture was added with water and dichloromethane, and further added with concentrated hydrochloric acid (1 ml). The organic layer was washed with diluted hydrochloric acid and brine and, after dried, the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt:n-hexane=1:40) to give s-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-nitrophenylthiophenol (Compound 32, 112.3 mg, 25%).

^{1}H-NMR $CDCl_3$: 8.23 (dd, 1H, 8.1Hz, 1.5Hz), 7.52 (d, 1H, 1.8Hz), 7.40 (d, 1H, 8.1Hz), 7.35 (m, 1H), 7.29 (dd, 1H, 8.1Hz, 1.8Hz), 7.20 (m, 1H), 6.90 (dd, 1H, 8.1Hz, 1.1Hz), 1.72 (s, 4H), 1.32 (s, 6H), 1.27 (s, 6H)

[0063] Compound 32 (275.3 mg, 0.807 mmol) was suspended in water (5 ml) and ethanol (10 ml), and added with concentrated hydrochloric acid (0.5 ml). Iron powder (210 mg) was added to this mixture, and heated under reflux for 5 minutes. The reaction mixture was filtered to removed solid materials, and the filtrate was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and, alter dried, the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt:n-hexane=1:40) to give s-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-aminothiophenol (Compound 33, 91.4 mg, 36%).

^{1}H-NMR $CDCl_3$: 7.43 (dd, 1H, 7.7Hz, 1.5Hz), 7.21 (m, 1H), 7.14 (d, 1H, 8.4Hz), 7.10 (d, 1H, 2.2Hz), 6.77 (m, 3H), 4.30 (brs, 2H), 1.64 (s, 4H), 1.22 (s, 6H), 1.20 (s, 6H)

[0064] Compound 33 (91.4 mg, 0.294 mmol) was dissolved in dried benzene (5 ml), and added with pyridine (0.2 ml, 2.5 mmol). To this solution, terephthalic acid monomethyl ester chloride (76 mg, 0.38 mmol) was added, and stirred at room temperature for 18 hours. The reaction mixture was added with ice water and dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried, and the solvent was evaporated to give a crude product (146.8 mg). This crude product was purified by silica gel column chromatography (AcOEt:n-hexane=1:20 → 1:10) to give methyl 4-[2-(s-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalenyl)amino)carbamoyl]benzoate (Compound 34, 123.7 mg, 89%).

^{1}H-NMR $CDCl_3$: 9.03 (brs, 1H), 8.65 (d, 1H, 7.0Hz), 8.05 (d, 2H, 8.8Hz), 7.66 (dd, 1H, 7.7Hz, 1.5Hz), 7.63 (d, 2H, 8.8Hz), 7.51 (m, 1H), 7.18 (m, 3H), 7.10 (d, 1H, 1.8Hz), 6.83 (dd, 1H, 8.4Hz, 2.2Hz), 3.95 (s, 3H), 1.61 (s, 4H), 1.20 (s, 6H), 1.13 (s, 6H)

[0065] Polyphosphoric acid (1.48 g) was added to Compound 34 (46.8 mg, 0.099 mmol), and stirred at 120°C for 45 minutes. The reaction mixture was added with water, and extracted with dichloromethane. The organic layer was dried, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt:n-hexane=1:40) to give methyl 4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,f][1,4]thiazepin-11-yl]benzoate (Compound 35, 27.3 mg, 61%).

^{1}H-NMR $CDCl_3$: 8.09 (d, 2H, 8.4Hz), 7.90 (d, 2H, 8.4Hz), 7.48 (dd, 1H, 7.7Hz, 1.5Hz), 7.44 (s, 1H), 7.38 (d, 2H, 7.7Hz), 7.34 (m, 1H), 7.13 (m, 1H), 7.03 (s, 1H), 3.96 (s, 3H), 1.64 (m, 4H), 1.31 (s, 3H), 1.28 (s, 3H), 1.13 (s, 3H), 1.06 (s, 3H)

[0066] Compound 35 (26.4 mg, 0.058 mmol) was suspended in ethanol (5 ml) and sodium hydroxide (1 ml), and stirred at room temperature for 40 minutes. The reaction mixture was acidified with 2N hydrochloric acid, and extracted with dichloromethane. The organic layer was washed with water and saturated brine, and alter dried, the solvent was concentrated under reduced pressure to give a compound of the present invention, 4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,f][1,4]thiazepin-11-yl]benzoic acid (HX 630, Compound 36, 24.9 mg, 97%). The product was recrystallized from a mixture of ethanol/water to give purified compound. m.p. 299°C

^{1}H-NMR $CDCl_3$: 8.17 (d, 2H 8.4Hz), 7.94 (d, 2H, 8.4Hz), 7.48 (dd, 1H, 7.7Hz, 1.1Hz), 7.45 (s, 1H), 7.37 (m, 2H), 7.13 (m, 1H), 7.04 (s, 1H), 1.65 (m, 4H), 1.31 (s, 3H), 1.28 (s, 3H), 1.15 (s, 3H), 1.07 (s, 3H)

Example 8: Preparation of 4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,e]azepin-11-yl]benzoic acid (HX640)

[0067] 5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalene (10.0 g, 53.2 mmol) and o-nitrobenzoic acid chloride (9.4 g, 50.5 mmol) were dissolved in dichloromethane (50 ml), and added with $AlCl_3$ (14.3 g) portionwise, and the reaction mixture was heated under reflux for 1 hour and 30 minutes. The reaction mixture was poured into water and extracted with dichloromethane, and alter dried, the solvent was evaporated to give a crude product (21.59 g). The product was purified by silica gel column chromatography (AcOEt:n-hexane=1:10) to give (5,5,8,8-tetramethyl-5,6,7,8- tetrahydro-2-naphthyl)carbonyl-2-nitrobenzene (Compound 37, 7.5 g, 42%). This product was further recrystallized from n-hexane.

^{1}H-NMR $CDCl_3$: 8.23 (d, 1H, 8.1Hz), 7.84 (s, 1H), 7.75 (t, 1H, 6.2Hz), 7.69 (t, 1H, 7.0Hz), 7.48 (dd, 1H, 7.7Hz, 1.5Hz), 7.34 (m, 2H), 1.69 (s, 4H), 1.28 (s, 6H), 1.26 (s, 6H)

[0068] Compound 37 (262.1 mg, 0.78 mmol) was dissolved in ethanol (10 ml), added with iron powder (313 mg) and then with concentrated hydrochloric acid (2.0 ml), and the reaction mixture was heated under reflux for 15 minutes. The reaction mixture was filtered, and the filtrate was extracted with added ethyl acetate. After dried, the solvent was evaporated to give (5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl-2-aniline (Compound 38, 242.9 mg, 100%).

^{1}H-NMR $CDCl_3$: 7.61 (d, 1H, 1.8Hz), 7.51 (d, 1H, 8.1Hz), 7.41 (dd, 1H, 8.1Hz, 1.8Hz), 7.37 (d, 1H, 8.1Hz), 7.29 (m, 1H), 6.74 (d, 1H, 8.1Hz), 6.61 (t, 1H, 8.1Hz), 1.72 (s, 4H), 1.32 (s, 6H), 1.29 (s, 6H)

[0069] Compound 38 (67.3 mg, 0.22 mmol) was dissolved in diethyl ether (2 ml), added with $LiAlH_4$ (41.3 mg, 1.09 mmol, suspended in 8 ml of diethyl ether), and heated under reflux for 19 hours. The reaction mixture was treated by a conventional manner, and the resulting crude product was purified by silica gel column chromatography (AcOEt:n-hexane=1:40-1:20) to give 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthylmethyl)aniline (Compound 39, 34.9 mg, 54%).

^{1}H-NMR $CDCl_3$: 7.20 (d, 1H, 8.1Hz), 7.15 (d, 1H), 7.09 (m, 1H), 7.05 (m, 1H), 6.89 (dd, 1H, 8.1Hz), 6.77 (td, 1H, 7.7Hz), 6.70 (d, 1H, 7.7Hz), 3.86 (s, 3H), 3.70 (brs, 2H), 1.66 (s, 4H), 1.25 (s, 6H), 1.24 (s, 6H)

[0070] Compound 39 (88.5 mg, 0.30 mmol) was dissolved in dried benzene (4 ml), and added with pyridine (0.2 ml, 2.5 mmol). Terephthalic acid monomethyl ester chloride (73.7 mg, 0.37 mmol) was added to this solution, and the reaction mixture was stirred at room temperature for 1 hour and 30 minutes. The reaction mixture was added with ice water and 2N HCl, and extracted with ethyl acetate. Alter dried, the solvent was evaporated, and the residue was purified by silica gel column chromatography to give methyl 4-[2-(2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthylmethyl)aminocarbonyl]benzoate (Compound 40, 115.1 mg, 84%).

^{1}H-NMR $CDCl_3$: 8.13 (d, 1H, 8Hz), 7.99 (d, 2H, 8.4Hz), 7.62 (brs, 1H), 7.38 (d, 2H, 8.4Hz), 7.30 (m, 3H), 7.21 (t, 1H, 7.7Hz), 7.11 (d, 1H), 6.90 (dd, 1H, 8.1Hz), 4.04 (s, 2H), 3.95 (s, 3H), 1.68 (m, 4H), 1.29 (s, 6H), 1.15 (s, 6H)

[0071] Polyphosphoric acid (1.56 g) was added to Compound 40 (103.4 mg, 0.227 mmol), and stirred at 110°C for 45 minutes. The reaction mixture was added with water, and extracted with dichloromethane. The organic layer was dried, and the solvent was evaporated. The residue was purified by silica gel column chromatography (AcOEt:n-hexane=1:20) to give methyl 4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,e]azepin-11-yl]benzoate (Compound 41, 78.3 mg, 79%).

^{1}H-NMR $CDCl_3$: 8.11 (d, 2H, 8.4Hz), 7.96 (d, 2H, 8.4Hz), 7.43 (brd, 1H, 8Hz), 7.25 (m, 2H), 7.22 (s, 1H), 7.17 (t, 1H, 7.3Hz), 7.08 (s, 1H), 3.96 (s, 3H), 3.70 (brs, 1H), 3.67 (brs, 1H), 1.64 (brs, 4H), 1.40 (brs, 3H), 1.30 (brs, 3H), 1.15 (brs, 3H), 1.04 (brs, 3H)

[0072] Compound 41 (78.3 mg, 0.179 mmol) was suspended in a mixture of ethanol (10 ml) and 2N NaOH (2 ml), and stirred at room temperature for 1 hour. The reaction mixture was acidified with 2N HCl, and extracted with dichloromethane. The organic layer was dried, and the solvent was evaporated to give 4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,e]azepine-11-yl]benzoic acid (HX640, Compound 42, 73.6 mg, 97%). The product was recrystallized from a mixture of ethanol/water to give purified compound. m.p. >300°C

^{1}H-NMR DMSO-d_6 (120°C): 8.05 (d, 2H, 8.4Hz), 7.89 (d, 2H, 8.4Hz), 7.39 (s, 1H), 7.33 (m, 2H), 7.26 (td, 1H, 7.3Hz, 1.5Hz), 7.16 (td, 7.3Hz, 1.5Hz), 7.09 (s, 1H), 3.69 (s, 2H), 1.66 (m, 4H), 1.32 (s, 6H), 1.11 (s, 6H)
Anal. Calc. for $C_{29}H_{29}NO_2$ C:82.24, H:6.90, N:3.31; Found C:82.30, H:6.98, N:3.02

Example 9: Preparation of 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX800)

[0073] 1,2,3,4-Tetrahydro-1,1,4,4-tetramethylnaphthalene (10.0 g, 53.2 mmol) and terephthalic acid monomethyl ester chloride (10.0 g, 50.5 mmol) were dissolved in dichloromethane (50 ml), and added with $AlCl_3$ (14.3 g, 107.5 mmol) over 10 minutes under ice cooling. After refluxed for 1 hour, the reaction mixture was poured into ice water, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and after dried, the layer was concentrated to give methyl 4-[(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoate (Compound 43, 18.5 g, 99%). A part of the product was recrystallized from ethyl acetate.

^{1}H-NMR $CDCl_3$: 8.15 (d, 2H, 8.8Hz), 7.83 (d, 2H, 8.4Hz), 7.79 (d, 1H, 1.8Hz), 7.54 (dd, 1H, 8.1Hz, 1.8Hz), 7.41 (d, 1H, 8.4Hz), 3.97 (s, 3H), 1.72 (s, 4H), 1.32 (s, 6H), 1.29 (s, 6H)

[0074] Compound 43 (693 mg, 1.98 mmol) was dissolved in concentrated H_2SO_4 (5 ml), and added with KNO_3 (240 mg, 2.37 mmol) under ice cooling. After 1 hour, the reaction mixture was poured into ice water, and extracted with dichloromethane. The organic layer was washed with saturated aqueous sodium hydrogencarbonate, water and saturated brine, dried and then concentrated. The residue was recrystallized from ethyl acetate to give methyl 4-[3-nitro-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylcarbonyl]benzoate as colorless needles (Compound 44, 414 mg, 53%).

^{1}H-NMR $CDCl_3$: 8.16 (s, 1H), 8.11 (d, 2H, 8.4Hz), 7.81 (d, 2H, 8.4Hz), 7.38 (s, 1H), 3.94 (s, 3H), 1.77 (s, 4H), 1.39 (s, 6H), 1.31 (s, 6H)

[0075] Compound 45 (318.5 mg, 0.806 mmol) was suspended in water (5 ml) and ethanol (10 ml), and added with concentrated hydrochloric acid (1.0 ml). The mixtue was added with iron powder (317 mg) and heated under reflux for 50 minutes. Then, the reaction mixture was filtered to remove solid materials. The filtrate was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine. After dried, the organic layer was concentrated to give methyl 4-[3-amino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoate as yellow crystals (Compound 46, 279.2 mg, 95%).

^{1}H-NMR $CDCl_3$: 8.14 (d, 2H, 8.4Hz), 7.69 (d, 2H, 8.8Hz), 7.31 (s, 1H), 6.67 (s, 1H), 5.90 (brs, 2H), 3.97 (s, 3H), 1.65 (m, 4H), 1.28 (s, 6H), 1.11 (s, 6H)

[0076] Pyridine (5 ml) was added to Compound 46 (70 mg, 0.19 mmol) and glycine methyl ester hydrochloride (38.3 mg, 0.31 mmol), and the mixture was refluxed for 16 hours. The reaction mixture was added with diluted hydrochloric acid, and extracted with dichloromethane. The organic layer was washed with water and saturated brine, dried and then

concentrated to give a residue (72.3 mg). The residue was purified by silica gel column chromatography (AcOEt:n-hexane=1:4) to give methyl 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoate (Compound 47, 34.7 mg, 45%). The starting material (23.1 mg) was also recovered (33%).

^{1}H-NMR $CDCl_3$: 8.06 (d, 2H, 8.8Hz), 7.66 (m, 3H), 7.16 (s, 1H), 6.96 (s, 1H), 4.36 (brs, 2H), 3.95 (s, 3H), 1.70 (m, 4H), 1.33 (s, 6H), 1.16 (s, 6H)

[0077] Compound 47 (32.6 mg, 0.08 mmol) was suspended in ethanol (5 ml) and 2N NaOH (1 ml), and the suspension was stirred at room temperature for 20 minutes. The reaction mixture was acidified with 2N hydrochloric acid, and extracted with dichloromethane. The organic layer was washed with water and saturated brine, and dried and then concentrated to give 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX800, Compound 48, 26.0 mg, 83%). A part of the product was recrystallized from methanol/hexane. m.p. > 300°C MS M^+ 390

^{1}H-NMR $CDCl_3$: 8.23 (brs, 1H), 8.12 (d, 2H, 8.4Hz), 7.69 (d, 2H, 8.4Hz), 7.17 (s, 1H), 7.01 (s, 1H), 4.38 (brs, 2H), 1.71 (s, 4H), 1.34 (s, 6H), 1.17 (s, 6H)

Example 10: Preparation of 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-1-methyl-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX801)

[0078] NaH (60% in oil, 7.1 mg, 0.18 mmol, 2 eq) was washed with hexane and dried, and then added with the methyl 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoate (36 mg, 0.089 mmol), dissolved in DMF (4 ml), which was obtained in Example 9. The mixture was stirred at room temperature for 10 minutes, and the mixture was added with CH_3I (0.02 ml, 0.36 mmol, 4 eq) and then further stirred for 2 hours and 30 minutes. The reaction mixture was poured into ice water, and extracted with dichloromethane. The organic layer was washed with water and saturated brine, and dried and then concentrated. The residue was purified by silica gel column chromatography (AcOEt:n-hexane=1:1) to give methyl 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-1-methyl-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoate (Compound 49, 21.8 mg, 59%).

^{1}H-NMR $CDCl_3$: 8.07 (d, 2H, 8.4Hz), 7.74 (d, 2H, 8.4Hz), 7.21 (s, 1H), 7.13 (s, 1H), 4.82 (d, 1H, 10.3Hz), 3.95 (s, 3H), 3.86 (d, 1H, 10.6Hz), 3.40 (s, 3H), 1.71 (m, 4H), 1.38 (s, 3H), 1.31 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H)

[0079] Compound 49 (29.6 mg, 0.07 mmol) was suspended in ethanol (3 ml) and 2N NaOH (1 ml), and the suspension was stirred at room temperature for 40 minutes. The reaction mixture was acidified with 2N HCl, and extracted with dichloromethane. The organic layer was washed with water and saturated brine, and dried and then concentrated to give 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-1-methyl-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX801, Compound 50, 23.5 mg, 83%). A part of the product was recrystallized from ethyl acetate/hexane. m.p. > 300°C

^{1}H-NMR $CDCl_3$: 8.13 (d, 2H, 8.8Hz), 7.77 (d, 2H, 8.4Hz), 7.22 (s, 1H), 7.14 (s, 1H), 4.84 (d, 1H, 10.6Hz), 3.88 (d, 1H, 10.6Hz), 3.41 (s, 3Hz), 1.72 (m, 4H), 1.39 (s, 3H), 1.32 (s, 3H), 1.21 (s, 3H), 1.15 (s, 3H)
Anal. Calc. for $C_{25}H_{28}N_2O_3$ C:74.23, H:6.98, N:6.93; Found C:74.19, H:6.97, N:6.63

Example 11: Preparation of 4-[3(S)-methyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX810)

[0080] Pyridine (5 ml) was added to the methyl 4-[3-amino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoate (188 mg, 0.515 mmol) obtained in Example 9 and L-alanine ethyl ester hydrochloride (177 mg, 0.77 mmol, 1.5 eq), and the mixture was refluxed for 16 hours. The reaction mixture was added with diluted hydrochloric acid, and then extracted with dichloromethane. The organic layer was washed with water and saturated brine, and dried and then concentrated. The residue was purified by silica gel column chromatography (AcOEt:n-hexane=1:3) to give methyl 4-[3(S)-methyl-1,3- dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoate (Compound 51, 25.6 mg, 12%).

^{1}H-NMR $CDCl_3$: 8.06 (d, 2H, 8.4Hz), 7.67 (d, 2H, 8.4Hz), 7.17 (s, 1H), 6.97 (s, 1H), 3.94 (s, 3H), 3.84 (q, 1H, 6.6Hz), 1.74 (d, 3H, 6.6Hz), 1.71 (m, 4H), 1.34 (s, 3H), 1.31 (s, 3H), 1.19 (s, 3H), 1.12 (s, 3H)

[0081] Compound 51 (15.1 mg, 0.036 mmol) was suspended in ethanol (3 ml) and 2N NaOH (1 ml), and stirred at room temperature for 40 minutes. The reaction mixture was acidified with 2N HCl, and extracted with dichloromethane.

The organic layer was washed with water and saturated brine, and dried and then concentrated to give 4-[3(S)-methyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX810, Compound 52, 14.9 mg, 100%). A part of the product was recrystallized from ethyl acetate/hexane. m.p. > 300°C

^{1}H-NMR $CDCl_3$: 8.11 (d, 2H, 8.4Hz), 7.95 (brs, 1H), 7.70 (d, 2H, 8.4Hz), 7.18 (s, 1H), 7.00 (s, 1H), 3.85 (q, 1H, 6.6Hz), 1.75 (d, 3H, 6.6Hz), 1.71 (m, 4H), 1.35 (s, 3H), 1.32 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H)
Anal. Calc. for $C_{25}H_{28}N_2O_3$ C:74.23, H:6.98, N:6.93; Found C:74.19, H:7.18, N:6.66

Example 12: Preparation of 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-1-isopropyl-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX803)

[0082] NaH (60% in oil, 4.7 mg, 0.12 mmol, 2 eq) was washed with hexane and dried, and then added with the methyl 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoate (24 mg, 0.059 mmol), dissolved in DMF (6 ml), which was obtained in Example 9. The reaction mixture was stirred at room temperature for 15 minutes, added with 2-iodopropane (0.02 ml, 0.24 mmol, 4 eq), and then further stirred for 4 hours. The reaction mixture was poured into ice water, and extracted with dichloromethane. The organic layer was washed with water and saturated brine, and dried and then concentrated. The residue was purified by silica gel column chromatography (AcOEt:n-hexane=1:5) to give methyl 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-1-isopropyl-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoate (Compound 53, 6.4 mg, 24%).

^{1}H-NMR $CDCl_3$: 8.07 (d, 2H, 8.4Hz), 7.74 (d, 2H, 8.4Hz), 7.31 (s, 1H), 7.10 (s, 1H), 4.73 (d, 1H, 10.3Hz), 4.57 (septet, 1H, 7.0Hz), 3.95 (s, 3H), 3.83 (d, 1H, 10.3Hz), 1.72 (m, 4H), 1.52 (d, 3H, 6.6Hz), 1.38 (s, 3H), 1.32 (s, 3H), 1.21 (s, 3H), 1.18 (d, 3H, 7.0Hz), 1.13 (s, 3H)

[0083] Compound 53 (6.4 mg, 0.014 mmol) was suspended in ethanol (4 ml) and 2N NaOH (0.5 ml), and stirred at room temperature for 2 hours. The reaction mixture was acidified with 2N HCl, and extracted with dichloromethane. The organic layer was washed with water and saturated brine, and dried and then concentrated to give 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-1-isopropyl-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX803, Compound 54, 6.2 mg, 100%). A part of the product was recrystallized from ethyl acetate/hexane. m.p. 275°C

^{1}H-NMR $CDCl_3$: 8.13 (d, 2H, 8.4Hz), 7.78 (d, 2H, 8.1Hz), 7.32 (s, 1H), 7.11 (s, 1H), 4.77 (d, 1H, 10.3Hz), 4.58 (septet, 1H, 7.0Hz), 3.85 (d, 1H, 10.3Hz), 1.73 (m, 4H), 1.53 (d, 3H, 7.0Hz), 1.39 (s, 3H), 1.32 (s, 3H), 1.22 (s, 3H), 1.19 (d, 3H, 7.3Hz), 1.14 (s, 3H)

Example 13: Preparation of 4-[1-benzyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX805)

[0084] NaH (60% in oil, 6.1 mg, 0.15 mmol, 2 eq) was washed with hexane and dried, and then added with the methyl 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoate (31.9 mg, 0.076 mmol), dissolved in DMF (3 ml), which was obtained in Example 9. The reaction mixture was stirred at room temperature for 20 minutes, added with benzyl bromide (0.035 ml, 0.30 mmol, 4 eq) and then further stirred for 1 hour. The reaction mixture was poured into ice water, and extracted with dichloromethane. The organic layer was washed with water and saturated brine, and dried and then concentrated. The residue was recrystallized from ethyl acetate/dichloromethane to give methyl 4-[1-benzyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoate (Compound 55, 23.3 mg, 60%).

^{1}H-NMR $CDCl_3$: 8.03 (d, 2H, 8.4Hz), 7.51 (d, 2H, 8.4Hz), 7.25 (s, 1H), 7.16 (m, 3H), 7.06 (m, 2H), 4.89 (d, 1H, 10.3Hz), 4.87 (d, 1H, 15.4Hz), 3.97 (d, 1H, 10.3Hz), 3.95 (s, 3H), 1.66 (s, 4H), 1.23 (s, 3H), 1.20 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H)

[0085] Compound 55 (19.1 mg, 0.035 mmol) was suspended in ethanol (6 ml) and 2N NaOH (1 ml), and the suspension was stirred at 70°C for 2 hours. The reaction mixture was acidified with 2N HCl, and extracted with dichloromethane. The organic layer was washed with water and saturated brine, and dried and then concentrated to give 4-[1-benzyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX805, Compound 56, 12.5 mg, 72%). A part of the product was recrystallized from ethyl acetate/dichloromethane. m.p. > 300°C

^{1}H-NMR $CDCl_3$: 8.08 (d, 2H, 8.8Hz), 7.55 (d, 2H, 8.4Hz), 7.16 (m, 3H), 7.07 (m, 2H), 7.00 (s, 1H), 5.45 (d, 1H, 14.7Hz), 4.91 (d, 1H, 10.3Hz), 4.88 (d, 1H, 14.3Hz), 3.99 (d, 1H, 10.3Hz), 1.65 (m, 4H), 1.23 (s, 3H), 1.21 (s, 3H),

1.12 (s, 3H), 1.09 (s, 3H)

Anal. Calc. for $C_{31}H_{32}N_2O_3$ C:77.47, H:6.71, N:5.83; Found C:77.27, H:6.80, N:5.70

Example 14: Preparation of 4-[3(S)-benzyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX850)

[0086] $SOCl_2$ (4 ml) was added to Fmoc-(L)-phenylalanine (272 mg, 0.70 mmol), and the mixture was refluxed for 30 minutes. The $SOCl_2$ was evaporated under reduced pressure, and the reaction mixture was dried sufficiently. The residue was added with methyl 4-[3-amino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylcarbonyl]benzoate (89 mg, 0.244 mmol) and DMAP (12 mg), and further added with anhydrous benzene (10 ml) and pyridine (0.5 ml). This mixture was stirred at room temperature for 50 minutes, acidified with 2N HCl, and then extracted with dichloromethane. The organic layer was washed with water and saturated brine, dried over Na_2SO_4, and then concentrated. The residue was purified by silica gel column chromatography (AcOEt:n-hexane=1:30) to give methyl 4-[[3-N-(N- α -9-fluorenylmethoxycarbonyl-L-phenylalanyl)amido-5,5,8,8-tetrahydro-2-naphthyl]carbonyl]benzoate (Compound 57, 117.8 mg, 99%).

^{1}H-NMR $CDCl_3$: 11.14 (s, 1H), 8.61 (s, 1H), 8.08 (d, 2H, 8.1Hz), 7.75 (d, 2H, 7.3Hz), 7.62 (m, 3H), 7.52 (m, 2H), 7.40 (m, 3H), 7.24 (m, 5H), 7.11 (d, 1H), 5.43 (d, 1H), 4.65 (d, 1H), 4.39 (m, 1H), 4.37 (m, 1H), 4.19 (m, 1H), 3.97 (s, 3H), 3.28 (m, 1H), 3.19 (m, 1H), 1.70 (m, 4H), 1.36 (s, 6H), 1.14 (s, 6H)

[0087] A mixture of Compound 57 (82.3 mg, 0.11 mmol), dichloromethane (4 ml) and piperidine (1 ml) was stirred at room temperature for 40 minutes. The solvent was evaporated under reduced pressure to dryness, and the residue was added with butanol (10 ml) and acetic acid (0.5 ml), and stirred at 80°C for 2 hours. The reaction mixture was added with aqueous sodium hydrogencarbonate, and extracted with dichloromethane. The extract was purified by silica gel column chromatography (AcOEt:n-hexane=1:10) to give methyl 4-[3(S)-benzyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoate (Compound 58, 48.4 mg, 92%).

^{1}H-NMR $CDCl_3$: 8.38 (brs, 1H), 8.03 (d, 2H, 8.4Hz), 7.58 (d, 2H, 8.4Hz), 7.42 (d, 2H, 7.3Hz), 7.32 (t, 2H, 7.3Hz), 7.23 (t, 1H, 7.0Hz), 7.10 (s, 1H), 7.00 (s, 1H), 3.93 (s, 3H), 3.87 (m, 1H), 3.63 (m, 2H), 1.68 (m, 4H), 1.34 (s, 3H), 1.31 (s, 3H), 1.16 (s, 3H), 1.10 (s, 3H)

[0088] Compound 58 (28.6 mg, 0.06 mmol) was suspended in ethanol (5 ml) and 1N KOH (2 ml), and the suspension was stirred at room temperature for 30 minutes. The reaction mixture was acidified with 2N HCl, and extracted with dichloromethane. The organic layer was dried and concentrated to give 4-[3(S)-benzyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX850, Compound 59, 24.8 mg, 89%). A part of the product was recrystallized from dichloromethane/hexane.

^{1}H-NMR $CDCl_3$: 8.27 (brs, 1H), 8.09 (d, 2H, 8.1Hz), 7.62 (d, 2H, 8.1Hz), 7.42 (d, 2H, 7.3Hz), 7.33 (t, 2H, 8.1Hz), 7.23 (t, 1H), 7.13 (s, 1H), 6.98 (s, 1H), 3.87 (m, 1H), 3.62 (m, 2H), 1.69 (m, 4H), 1.34 (s, 3H), 1.31 (s, 3H), 1.18 (s, 3H), 1.11 (s, 3H)

Example 15: Test Example

[0089] Effects of the compounds of the above Examples 1 and 2 on cell differentiation inducing activity of retinoids were examined. Retinoic acid and Am80 (4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid) were used as retinoid compounds (agonists against all-trans retinoic acid receptor). Cell differentiation inducing ability of the above retinoids for promyelocytic leukemia cell strain HL-60 was determined in the presence and absence of the compounds of Examples 1 and 2 according to the method described in Japanese Patent Unexamined Publication (KOKAI) No. (Sho)61-76440/1986. Degree of differentiation into granulocytic cells was determined by observing nuclear morphology and measuring ability to reduce nitroblue tetrazolium (NBT). This method is well known in the art as a test capable of highly reflecting cell differentiation inducing activity of retinoids. The result are shown in Table 2 set out below (in the table, NTB positive ratio represents the ratio in percent of differentiated cells based on alive cells).

Table 2

Retinoid(M)	Test compound (M)	NBT positive ratio(%)
Retinoic acid	Absent	14
(1.1×10^{-9})	HX600 1.1×10^{-7}	68
	HX600 3.3×10^{-7}	76
	HX600 1.0×10^{-6}	69
Retinoic acid	Absent	36
(3.3×10^{-9})	HX600 1.1×10^{-7}	86
	HX600 3.3×10^{-7}	90
	HX600 1.0×10^{-6}	90
Retinoic acid	Absent	54
(1.0×10^{-8})	HX600 1.1×10^{-7}	91
	HX600 3.3×10^{-7}	91
	HX600 1.0×10^{-6}	91
Am80	Absent	15
(3.7×10^{-10})	HX600 1.0×10^{-9}	21
	HX600 1.0×10^{-8}	41
	HX600 1.0×10^{-7}	72
	HX600 1.0×10^{-6}	67
Am80	Absent	44
(1.1×10^{-9})	HX600 1.0×10^{-9}	48
	HX600 1.0×10^{-8}	65
	HX600 1.0×10^{-7}	90
	HX600 1.0×10^{-6}	93
Am80	Absent	53
(3.3×10^{-9})	HX600 1.0×10^{-9}	64
	HX600 1.0×10^{-8}	73
	HX600 1.0×10^{-7}	93
	HX600 1.0×10^{-6}	93
Am80	Absent	55
(1.0×10^{-8})	HX600 1.0×10^{-9}	69
	HX600 1.0×10^{-8}	80
	HX600 1.0×10^{-7}	91
	HX600 1.0×10^{-6}	95
Am80	Absent	
(3.3×10^{-10})	HX640 1.0×10^{-10}	44
	HX640 1.0×10^{-9}	46

	HX640 1.0×10^{-8}	75
	HX640 1.0×10^{-7}	89
	HX640 1.0×10^{-6}	85
Am80	Absent	
(1.1×10^{-10})	HX640 1.0×10^{-10}	7
	HX640 1.0×10^{-9}	5
	HX640 1.0×10^{-8}	24
	HX640 1.0×10^{-7}	69
Am80	Absent	21
(3.7×10^{-10})	LE135 1.1×10^{-7}	3
	LE135 3.3×10^{-7}	1.2
	LE135 1.0×10^{-6}	1.3
Am80	Absent	35
(1.1×10^{-9})	LE135 1.1×10^{-7}	23
	LE135 3.3×10^{-7}	5
	LE135 1.0×10^{-6}	2
Am80	Absent	51
(3.3×10^{-9})	LE135 1.1×10^{-7}	54
	LE135 3.3×10^{-7}	32
	LE135 1.0×10^{-6}	14
Am80	Absent	55
(1.0×10^{-8})	LE135 1.1×10^{-7}	62
	LE135 3.3×10^{-7}	51
	LE135 1.0×10^{-6}	34

[0090] When the compounds of the present invention were allowed to coexist with retinoic acid or Am80, ratios of differentiated cells were remarkably increased. Therefore, it is apparent that the compounds of the present invention enhanced cell differentiation inducing activity of retinoic acid or Am80. The compound LE135, used as control, is known as an antagonist of retinoid (Compound 16 in Eyrolles, L., et al., J. Med. Chem., 37, pp. 1508-1517, 1994: 4-(5H-7,8,9,10-tetra-hydro-5,7,7,10,10-pentamethylbenzo[e]naphto[2,3-b][1,4]diazepin-13-yl)benzoic acid), and corresponds to a structural isomer of compound HX600 of the present invention. When this compound was allowed to coexist with Am80, the cell differentiation inducing activity of Am80 was remarkably suppressed.

Example 16: Test Example

[0091] Effects of the compound of Example 10 (HX801) on cell differentiation inducing activity of retinoid were examined. Am80 was used as a retinoid compound, and the cell differentiation inducing activity of the above retinoid on promyelocytic leukemia cell strain HL-60 was determined in the presence or absence of the compound of HX801 according to the same method as Example 15. The results are shown in the following Table 3 (in the table, "-" represents the absence of the drug). When the compound of the present invention was allowed to coexist with Am80, the ratio of the differentiated cells was remarkably increased. These results clearly indicate that the cell differentiation inducing activity of Am80 was enhanced by the compound of the present invention.

Table 3

Am80 (M)	HX801 (M)	NBT Positive ratio (%)
—	—	1*
1.0×10^{-9}	—	48
3.3×10^{-10}	—	30
1.1×10^{-10}	—	5
3.7×10^{-11}	—	3
1.2×10^{-11}	—	0.6
—	1.0×10^{-6}	1.1
—	3.3×10^{-7}	0.3
—	1.1×10^{-7}	1.1
1.0×10^{-9}	1.0×10^{-6}	77
"	3.3×10^{-7}	76
"	1.1×10^{-7}	63
3.3×10^{-10}	1.0×10^{-6}	71
"	3.3×10^{-7}	55
"	1.1×10^{-7}	49
1.1×10^{-10}	1.0×10^{-6}	48
"	3.3×10^{-7}	28
"	1.1×10^{-7}	22
3.7×10^{-11}	1.0×10^{-6}	4.4
"	3.3×10^{-7}	2.3
"	1.1×10^{-7}	4
1.2×10^{-11}	1.0×10^{-6}	2
"	3.3×10^{-7}	2
"	1.1×10^{-7}	1.4

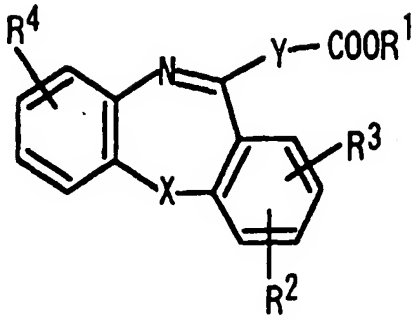
* Control

Industrial Applicability

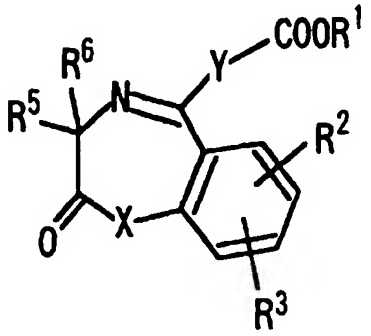
[0092] The compounds of the present invention enhance the action of retinoids such as retinoic acid, and are useful as medicaments for enhancing the activity of a retinoid.

Claims

1. A compound represented by the following general formula (I):



or the following general formula (II) or salts thereof:



wherein, R^1 represents hydrogen atom or a C_{1-6} alkyl group; R^2 and R^3 independently represent hydrogen atom or a C_{1-6} alkyl group, or R^2 and R^3 may combine together with the carbon atoms of the phenyl ring to which R^2 and R^3 bind to represent a 5- or 6-membered cycloalkyl group which may optionally be substituted with one or more C_{1-4} alkyl groups; R^4 represents hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, hydroxyl group, nitro group, or a halogen atom; R^5 represents hydrogen atom, a C_{1-6} alkyl group, or an aryl-substituted C_{1-6} alkyl group; R^6 represents hydrogen atom or a C_{1-6} alkyl group; X represents $-NR^7-$, -O-, $-CHR^7-$ or -S- in which R^7 represents hydrogen atom, a C_{1-6} alkyl group, or an aryl-substituted C_{1-6} alkyl group; and Y represents a phenylene group or a pyridinediyl group.

2. The compound according to claim 1 which is selected from the group consisting of the following compounds or a salt thereof:

4-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl]benzoic acid (HX600);
4-[5H-2,3-diisopropyl-5-methyldibenzo[b,e][1,4]diazepin-11-yl]benzoic acid (HX610);
4-[5H-2-tert-butyl-5-methyldibenzo[b,e][1,4]diazepin-11-yl]benzoic acid (HX511);
4-[5H-3,4-(1,4-butano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl]benzoic acid (HX545);
4-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyl-8-nitrodibenzo[b,e][1,4]-diazepin-11-yl]benzoic acid (HX531);
4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,f][1,4]oxazepin-11-yl]benzoic acid (HX620);
4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,f][1,4]thiazepin-11-yl]benzoic acid (HX630);
5-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl]-2-pyridinecarboxylic acid;
6-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl]-3-pyridinecarboxylic acid; and
4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo[b,e]azepin-11-yl]benzoic acid (HX640).

3. The compound according to claim 1 which is selected from the group consisting of the following compounds or a salt thereof:

4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX800);

4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-1-methyl-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX801);
4-[3(S)-methyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX810);
4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-1-isopropyl-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX803);
4-[1benzyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX805); and
4-[3(S)-benzyl-1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]benzoic acid (HX850).

4. A medicament comprising a compound or a physiologically acceptable salt thereof according to claim 1.

5. The medicament according to claim 4, wherein said medicament is in the form of a pharmaceutical composition comprising a compound or a physiologically acceptable salt thereof according to claim 1 together with one or more pharmaceutical additives.

6. The medicament according to claim 4, wherein said medicament is used as an agent for enhancing the activity of a physiologically active substance which exerts the physiological activity by binding to an intranuclear receptor that belongs to the intranuclear receptor super family.

7. The medicament according to claim 6, wherein the physiologically active substance is a retinoid compound.

8. A pharmaceutical composition comprising a compound according to claim 1 or a physiologically acceptable salt thereof together with a retinoid compound.

9. A method for enhancing the activity of a physiologically active substance which exerts the physiological activity by binding to an intranuclear receptor that belongs to the intranuclear receptor super family, which comprises a step of administering a compound of claim 1 or a physiologically acceptable salt thereof to a mammal.

10. The method according to claim 9, wherein the physiologically active substance is a retinoid compound.

11. The method according to claim 9, wherein the physiologically active substance is retinoic acid which inherently exist in the living body of said mammal.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP96/02709

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl[6] C07D243/10, 243/16, 223/18, 223/16, C07D267/14, 281/10, A61K31/55
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int. Cl[6] C07D243/10-16, C07D223/16, 18-26, C07D267/14, 16, C07D281/10-16, A61K31/55

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CASONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	Chemical & Parmaceutical Bulletin; Vol. 43 (No. 10), p. 1827-1829 (October, 1995)	1 - 8
X A	Journal of Medicinal Chemistry; Vol. 37 (No. 10), p. 1508-1517 (May 13, 1994)	1 2 - 8
X	Journal of Organic Chemistry; Vol. 37 (No. 24), p. 3755-3770 (1972) p. 3759 compound; 38a, 38b, preparation; page 3568, right column	1
X	Chemical Abstracts; Vol. 66, p. 1046 (1967), Abstract No. 10838a Abstract of Acta Chem. Scand. Vol. 20 (No. 6) p. 1631-44 (1966)	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
December 16, 1996 (16. 12. 96)	December 25, 1996 (25. 12. 96)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP96/02709

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9 - 11
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 9 to 11 pertain to methods for treatment of the human or animal body by surgery or therapy.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)